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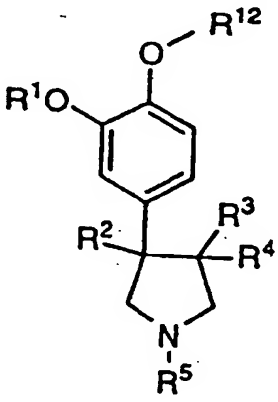
(57) Abstract

Novel pyrrolidine compounds of formula (I) which are useful for inhibiting the function of Type IV phosphodiesterase (PDE-IV) as wll as methods for making the same are disclosed. Applications in treating inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, are also disclosed.



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DESCRIPTION

3-(3,4-DIOXYPHENYL)-PYRROLIDINES AS TYPE IV PHOSPHODIESTERASE INHIBITORS FOR THE TREATMENT OF INFLAMMATORY DISEASES

Field of Invention

The present invention relates to novel pyrrolidine compounds which are useful for inhibiting the function of Type IV phosphodiesterase (PDE-IV) as well as methods for making the same and their applications in treating inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders.

Background of the Invention

Sites of chronic inflammation are characterized by the presence and activation of multiple types of inflammatory cells, particularly cells of lymphoid lineage (including T lymphocytes) and myeloid lineage (including granulocytes, macrophages and monocytes). Pro-inflammatory mediators, including cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), are produced by these activated cells. Accordingly, an agent which suppresses the activation of these cells or their production of pro-inflammatory cytokines would be useful in the therapeutic treatment of inflammatory diseases or other diseases involving elevated levels of cytokines.

Cyclic AMP has been shown to be a second messenger which mediates the biologic responses of cells to a wide range of extracellular stimuli. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated to convert ATP to cAMP. The actions of cAMP are terminated by cyclic nucleotide phosphodiesterases (PDEs) which hydrolyze the 3'-phosphodiesterase bond to form 5'-AMP, an inactive metabolite. In short, the intracellular enzyme family of PDEs regulates the level of cAMP in cells. Accordingly, the inhibition of PDE function would prevent the conversion of cAMP to the inactive metabolite 5'-AMP and, consequently, maintain higher cAMP levels (see Beavo and Houslay, Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action, Wiley, Chichester, pgs 3-14, 1990).

Elevated levels of cAMP in human myeloid and lymphoid lineage cells are associated with the suppression of cell activation. Type IV cAMP phosphodiesterase (PDE-IV) is a predominant PDE isotype in these cells and is thus a major mechanism of cAMP degradation. It is now recognized that inhibiting PDE-IV function can cause elevation of cAMP in these cells and suppression of cell activation (for review, see Torphy, et al, Novel phosphodiesterase inhibitors for the therapy of asthma, Drug News and Perspectives 6:203-214; Giembycz and Dent, Prospects for selective cyclic nucleotide phosphodiesterase inhibitors in the treatment of bronchial asthma, Clin Exp Allergy 22:337-344).

In particular, PDE-IV inhibitors have been shown to inhibit production of TNFα and partially inhibit IL-1β release by monocytes (see Semmler, et al, The specific type-IV phosphodiesterase inhibitor rolipram suppresses TNFα production by human mononuclear cells, Int J Immunopharmacol 15:409-413, 1993; Molnar-Kimber, et al, Differential regulation of TNF-α and IL-1β production from endotoxin stimulated human monocytes by phosphodiesterase inhibitors, Mediators of Inflammation 1:411-417, 1992). PDE-IV inhibitors have also been shown to inhibit the production of super oxide radicals from human polymorphonuclear leukocytes [see Verghese, et al, J Mol Cell Cardiol 12 (Suppl. II), sS.61; Nielson, et al, Effects of selective phosphodiesterase inhibitors on the polymorphonuclear leukocyte respiratory burst, J Allergy Clin Immunol 86:801-808, 1990]; to inhibit the release of vasoactive amines and prostanoids from human basophils (see Peachell, et. al., Preliminary identification and role of phosphodiesterase isozymes in human basophils, J Immunol 148:2503-2510, 1992); to inhibit respiratory bursts in eosinophils (see Dent, et el, Inhibition of eosinophil cyclic nucleotide PDE activity and opsonized zymosan stimulated respiratory burst by type IV-selective PDE inhibitors, Br J Pharmacol 103:1339-1346, 1991); and to inhibit the activation of human T-lymphocytes (see Robicsek, et. al., Multiple high-affinity cAMP-phosphodiesterases in human T-lymphocytes; Biochem Pharmacol 42:869-877, 1991).

Inflammatory cell activation and excessive or unregulated cytokine (e.g., TNFα and IL-1β) production are implicated in allergic, autoimmune or inflammatory diseases or disorders, such as rheumatoid arthritis, osteoarthritis, gouty arthritis, spondylitis, sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, toxic shock syndrome, asthma, chronic bronchitis, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, reperfusion injury of the myocardium, brain or extremities, fibrosis,

cystic fibrosis, keloid formation, scar formation, atherosclerosis, transplant rejection disorders such as graft vs. host reaction and allograft rejection, chronic granulonephritis, lupus, inflammatory bowel disease such as Crohn's disease and ulcerative colitis and inflammatory dermatoses such as atopic dermatitis, psoriasis or urticaria. Other conditions characterized by elevated cytokine levels include cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), AIDA, fever and myalgias due to infection, cerebral malaria, osteoporosis and bone resorption diseases, keloid formation, scar tissue formation or pyrexia.

In particular, TNFα has been implicated in various roles with respect to human acquired immune deficiency syndrome (AIDS). AIDS results from the infection of T-lymphocytes with Human Immunodeficiency Virus (HIV), although HIV also infects and is maintained in myeloid lineage cells. TNF has been shown to upregulate HIV infection in T-lymphocytic and monocytic cells (see Poli, et al, Tumor necrosis factor alpha functions in an autocrine manner in the induction of human immunodeficiency virus expression, Proc Natl Acad Sci 87:782-785, 1990).

Several properties of TNFα such as stimulation of collagenases, stimulation of angiogenesis in vivo, stimulation of bone resorption and ability to increase the adherence of tumor cells to endothelium are consistent with a role for TNF in the development and metastatic spread of cancer in the host. TNFα has recently been directly implicated in the promotion of growth and metastasis of tumor cells (see Orosz, et al, Enhancement of experimental metastasis by tumor necrosis factor, J Exp Med 177:1391-1398, 1993).

Accordingly, chemical compounds which selectively inhibit PDE-IV would be useful in the treatment of allergic or inflammatory diseases or other diseases associated with excessive or unregulated production of cytokines, such as TNF. In addition, PDE-IV inhibitors would be useful for treatment of diseases which are associated with elevated cAMP levels or PDE-IV function in a particular target tissue. For example, PDE-IV inhibitors could be used in the treatment of diabetes insipidus (Kidney Int. 37:362, 1990; Kidney Int. 35:494, 1989) and central nervous system disorders, such as depression and multi-infarct dementia (see Eckman, et al, Curr. Ther. Res. 43:291, 1988; Nicholson, Psychopharmacology 101:147, 1990). Another application involving the use of PDE-IV inhibitors concerns modulating

bronchodilatory activity via direct action on bronchial smooth muscle cells for the treatment of asthma.

Brief Description of the Drawings

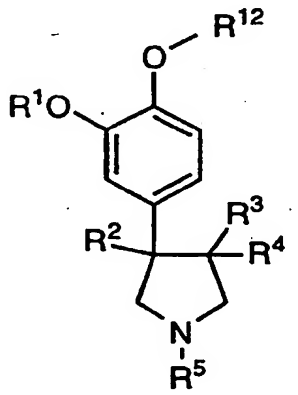
Fig. 1 sets forth the DNA sequence analysis of hPDE-M and hPDE-R.

Fig. 2 sets forth the site directed mutagenesis and assembly of PDE-IV E. coli expression construction.

Fig. 3 sets forth the site directed mutagenesis and assembly of PDE-IV baculovirus expression construction.

Detailed Description of the Invention

The present invention comprises the genus of compounds represented by Formula (I):



(I)

wherein

R^1 is alkyl, haloalkyl, cycloalkyl, bridged polycycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl or aryloxyalkyl;

R^2 is H, alkyl, haloalkyl, cycloalkyl, aryl, -CO-alkyl, -CO-cycloalkyl, -CO-aryl, -COO-alkyl, -COO-cycloalkyl, -COO-aryl, CH_2OH, CH_2-O-alkyl, -CHO, -CN, $-NO_2$ or SO_2R^{10};

R^3 is -CO-alkyl, -CO-haloalkyl, -CO-cycloalkyl, -COO-alkyl, -COO-cycloalkyl, -COOH, -CO-aryl, $-CONR^6R^7$, $-CH_2OH$, $-CH_2O$-alkyl, -CHO, -CN, $-NO_2$, $-NR^8COR^9$, $-NR^8SO_2R^{10}$ or $-SO_2R^{10}$;

R^4 is H, alkyl, haloalkyl, cycloalkyl, -CO-alkyl, -CO-haloalkyl, -CO-cycloalkyl, -COO-alkyl, -COO-cycloalkyl, -COOH, -CO-aryl, $-CONR^6R^7$, -CN, -CHO or SO_2R^{10};

R^5 is -CN or $-C(X)-R^{11}$ or SO_2R^{10};

R^6 and R^7 are independently selected from H, alkyl, cycloalkyl, aryl or aralkyl or R^6 and R^7 together form a 4- to 7-membered heterocyclic or carbocyclic ring;

R^8 is H, alkyl or cycloalkyl;

R^9 is alkyl, cycloalkyl, aryl, alkoxy, aralkoxy or $-NR^6R^7$;

R^{10} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl or $-NR^6R^7$;

R^{11} is H, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaryl, C_{1-6}alkoxy, aralkoxy, aryloxy or $-NR^6R^7$;

R^{12} is C_{1-3}alkyl, cyclopropyl or C_{1-3}haloalkyl; and

X is O or S.

As provided herein, the term "alkyl", alone or in combination, is defined herein to include straight chain or branched chain saturated hydrocarbon groups from C_1-C_7. The term "lower alkyl" is defined herein as C_1-C_4. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, n-butyl, n-hexyl, and the like. The term "haloalkyl" is defined herein as a lower alkyl substituted with one or more halogens. The term "cycloalkyl" is defined herein to include cyclic hydrocarbon radicals from

C_3-C_7. Exemplary cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclobutyl, and cyclopentyl.

The term "alkoxy", alone or in combination, is defined herein to include an alkyl group, as defined earlier, which is attached through an oxygen atom to the parent molecular subunit. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, isobutoxy, n-butoxy, and the like.

The term "aryl", alone or in combination, is defined herein as a monocyclic or polycyclic group, preferably a monocyclic or bicyclic group, i.e. phenyl or naphthyl, which can be unsubstituted or substituted, for example, with one or more and, in particular, one to three substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulfinyl and alkylsulfonyl. Exemplary aryl groups include phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 4-nitrophenyl, and the like.

The term "aralkyl" is defined herein as an alkyl group, as defined earlier, in which one of the hydrogen atoms is replaced by a phenyl group, an aryl or heteroaryl group as defined herein or a phenyl group carrying one or more substituents selected from, for example, halogen, alkyl, alkoxy and the like.

The term "aralkoxy", alone or in combination, is defined herein to include an aralkyl group, as defined earlier, which is attached through an oxygen atom to the parent molecular subunit. Exemplary aralkoxy groups include phenylmethoxy, phenylethoxy, phenylpropoxy and the like.

The term "heteroaryl" is defined herein as a 5-membered or 6-membered heterocyclic aromatic group which can optionally carry a fused benzene ring and which can be unsubstituted or substituted, for example, with one or more and, in particular, one to three substituents selected from halogen, alkyl, hydroxy, alkoxy, haloalkyl, nitro, amino, acylamino, alkylthio, alkylsulfinyl and alkylsulfonyl.

The term "halogen" is defined herein to include fluorine, chlorine, bromine and iodine.

The term "heteroaralkyl" is defined similarly as the term "aralkyl", however with the replacement of the aryl group with a heteroaryl group.

The term "bridged polycycloalkyl", as set forth herein, is intended to include bridged polycyclics of 6 to 12 carbons (e.g. bridged bicycloalkyls such as bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl and bicyclo[3.2.1]octyl.)

Those skilled in the art will recognize that stereocenters exist in compounds of Formula (I). Accordingly, the present invention includes all possible stereoisomers and geometric isomers of Formula (I) and includes not only racemic compounds but also the optically active isomers as well. In particular, it will be appreciated that positions 3 and 4 of the pyrrolidine ring of the compounds of Formula (I) are both chiral. Thus, the compounds of Formula (I) can exist in both cis and trans forms and each of these forms may comprise two enantiomers. Accordingly, each compound of Formula (I) may exist as one of four diastereoisomers. It will be further appreciated that Formula (I) does not show either the relative or absolute configuration of the 4 substituents at positions 3 and 4 of the pyrrolidine ring.

When a compound of Formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Carbon Compounds by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents by S. H. Wilen. Additionally, in situations where tautomers of the compounds of Formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.

In one preferred sub-class of compounds of Formula (I):

R^1 is alkyl, cycloalkyl, aralkyl or aryloxyaryl;

R^2 is hydrogen;

R^3 is -CO-alkyl, -COO-alkyl, -COOH, -CO-aryl, $-CONR^6R^7$; -CN, $-NO_2$, $-NR^8COR^9$ or $-NR^8SO_2R^{10}$;

R^4 is hydrogen, alkyl or -CO-alkyl;

R^5 is CN or $C(X)R^{11}$; and

R^{12} is C_{1-3}alkyl.

In another preferred sub-class of compounds of Formula (I):

R^1 is cycloalkyl, in particular cyclopentyl;

R^2 is hydrogen;

R^3 is COalkyl, CO_2H or CO_2alkyl, in particular $COCH_3$;

$R^4$is hydrogen or, particularly, alkyl such as methyl;

R^5 is CO_2alkyl, in particular CO_2CH_3; and

R^{12} is C_{1-3}alkyl, in particular methyl.

Particularly preferred are compounds as defined above in which R^1 is cyclopentyl.

Some specific compounds of Formula (I) are listed below, the synthesis of which was performed in accordance with the Example section set forth below.

cis-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-methoxycarbonyl-1-(1,1-dimethylethoxycarbonyl)-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-(3,4-dimethoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(hydroxymethyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(methoxycarbonyl)pyrrolidine;

trans-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

cis-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

trans-1-methoxycarbonyl-3-methoxycarbonyl-4-(3-phenylmethoxy-4-methoxyphenyl)pyrrolidine;

-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-methyl-4-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-(methoxycarbonyl)pyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-methoxycarbonyl-4-methylpyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethylcarbonyl-1-(methoxycarbonyl)pyrrolidine;

trans-1-methoxycarbonyl-3-nitro-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-cyano-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-nitropyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(phenylcarbonyl)pyrrolidine;

trans-1-methoxycarbonyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-methoxycarbonyl-4-methylpyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-methoxycarbonyl-4-methylpyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-imidazolylcarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-formyl-4-(methoxycarbonyl)pyrrolidine;

trans-1-formyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(1-methylethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-(methoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-methylethoxycarbonyl)pyrrolidine;

trans-3-carboxy-1-(methoxycarbonyl)-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-formylpyrrolidine;

trans-1-aminocarbonyl-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)pyrrolidine;

trans-3-aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-[(*N*-phenylmethyl)aminocarbonyl]pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-[*N*-(1,1-dimethylethoxycarbonyl)-*N*-methyl]-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(methylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)-4-*N*-(trifluoromethylsulfonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(phenylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxy)phenyl)-1-methoxycarbonyl-4-N-(methoxycarbonyl)pyrrolidine;

trans-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-1-aminothiocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

trans-1-cyano-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylethoxycarbonyl)pyrrolidine;

53-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-methoxycarbonyl-4-methylpyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methoxymethyl)pyrrolidine.

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(phenylcarbonyl) pyrrolidine:

3-(3-cyclopentoxy-4-methoxypheny)-1-(4-methoxy phenylcarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

1-(4-chlorophenylcarbonyl)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl) pyrrolidine

3-3-cyclopentoxy-methoxyphenyl)-1-(2-furyl carbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(4-iodo phenylcarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethoxycarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethyl ethoxycarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-formyl-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(methylsulfonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-imidazolyl carbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

1-aminocarbonly-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

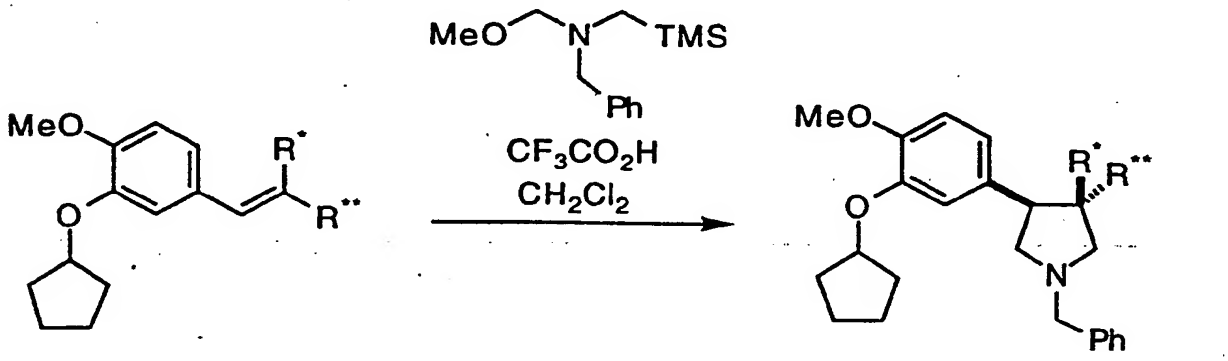
3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine

Generally, compounds of Formula (I) can be prepared according to the following synthesis schemes. In all of the schemes described below, it is well understood in the art that protecting groups are employed where necessary in accordance with general principles of chemistry. These protecting groups are removed in the final steps of the synthesis under basic, acidic, or hydrogenolytic conditions which will be readily apparent to those skilled in the art. By employing appropriate manipulation and protection of any chemical functionalities, synthesis of any compounds of the Formula (I) not specifically set forth herein can be accomplished by methods analogous to the schemes set forth below as well as those described in the Example section.

One method for the preparation of compounds having Formula (I) uses an azomethine ylide cycloaddition reaction for the synthesis of the pyrrolidine ring. *N*-benzyl-*N*-methoxymethyl-*N*-trimethylsilylmethylamine, prepared by the procedure described by Padwa and coworkers (*J. Org. Chem.* **1987**, *52*, 235), is reacted with an appropriately substituted olefin according to the procedure of Achiwa and coworkers (*Chem. Pharm. Bull.* **1985**, *33*, 2762).

Such a cycloaddition reaction proceeds with aryl-substituted olefins bearing an electron-withdrawing group. The olefin can be prepared by any of a number of methods available including Horner-Emmons and Wittig chemistry. The preferred

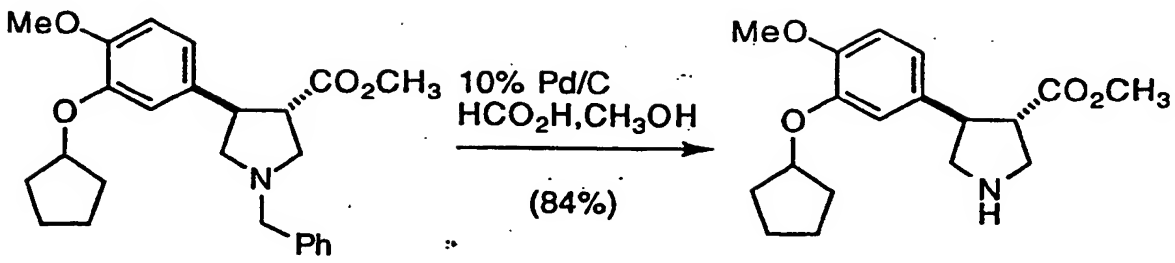
process for the cycloaddition reaction is in an inert solvent (e.g. methylene chloride, dioxane, tetrahydrofuran, toluene) under the influence of a suitable acid, such as trifluoroacetic acid, at temperatures ranging from -20–30 °C. Alternatively, one can affect the cycloaddition under the influence of lithium fluoride and sonication (Padwa, *vide supra*). For example, one particular approach for the cycloaddition reaction is shown below.

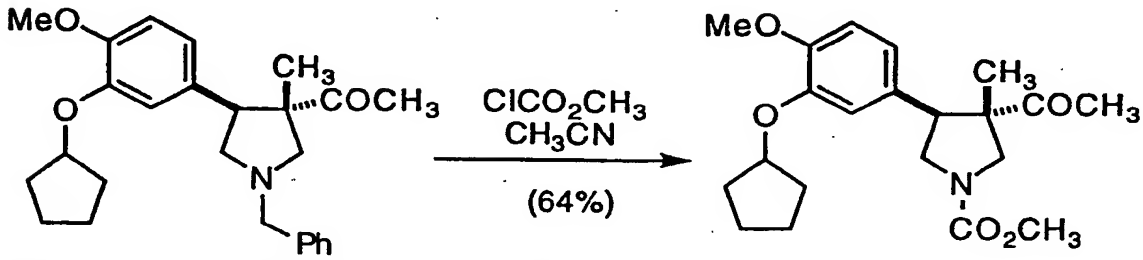


R^*	R^{**}	Yield (%)
CO_2CH_3	H	77
H	CO_2CH_3	86
H	NO_2	56
CH_3	$CO_2CH_2CH_3$	87

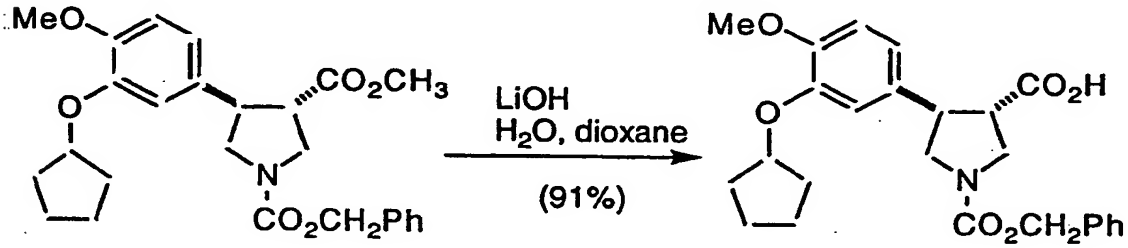
(R^* and R^{**} are intended only to designate examples of functional groups that can be used to facilitate the cycloaddition reaction. One skilled in the art of organic synthesis will appreciate that other functional groups at R^* and R^{**} are acceptable and that appropriate manipulation of R^* and R^{**} may be required to complete the synthesis of compounds of Formula (I).)

The pyrrolidines obtained from the azomethine ylide cycloaddition can be converted into compounds of Formula (I) by methods available to one who is skilled in the art of organic synthesis. Reductive debenzylation of the pyrrolidine can be carried out by transfer hydrogenation (4% HCO_2H/MeOH;10% Pd/C) at room temperature. Other suitable methods for debenzylation (10% Pd/C, 50 psi H_2, acetic acid) can also be used. The free pyrrolidine can then be acylated under the influence of a suitable base and acylating reagent. Alternatively, debenzylation/*N*-acylation can be affected in one operation by reacting the 1-(phenylmethyl)pyrrolidine with a chloroformate in a suitable solvent (e.g., dichloroethane, acetonitrile, etc.) at temperatures between 30-100 °C. Some specific examples of these methods are shown below.

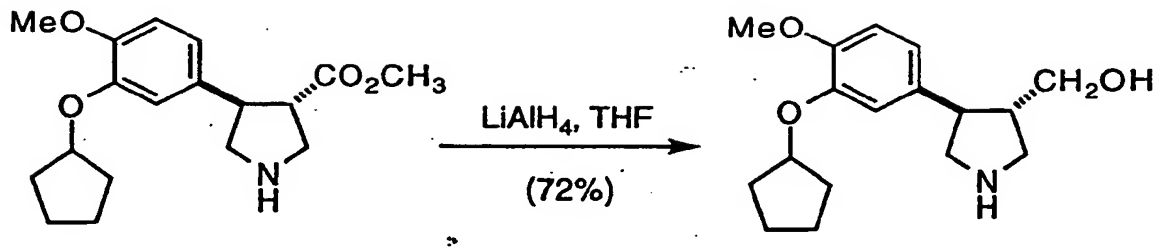


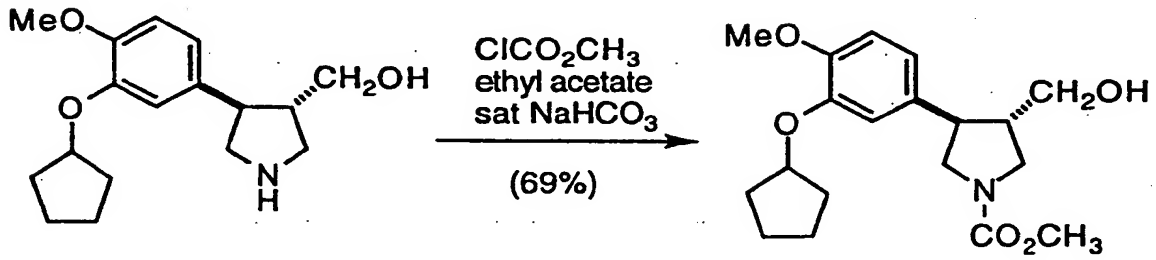


Compounds of Formula (I) in which R^3 is COOH may be obtained by saponification of the corresponding alkyl ester. The preferred method for saponification uses an alkali metal hydroxide (e.g., LiOH) at 0–23 °C in an aqueous ethereal solvent system (e.g., 1:1, 1,4-dioxane:H_2O). A specific example of this chemistry is shown below.

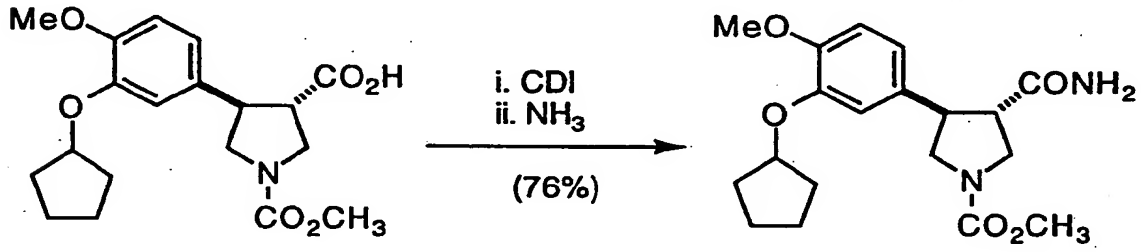


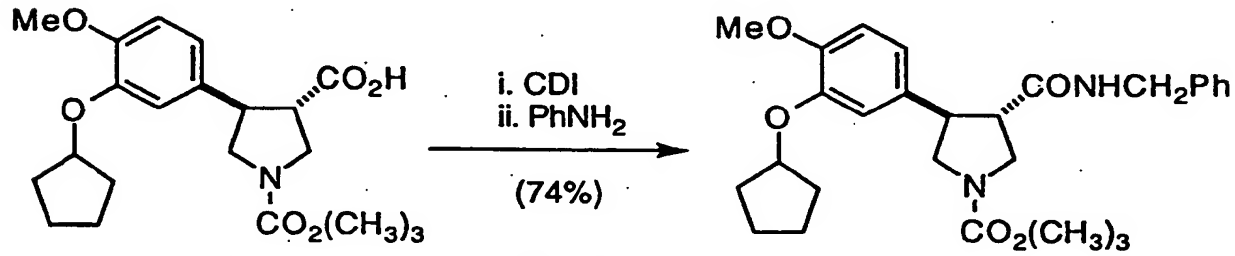
Compounds of Formula (I) in which R^3 is CH_2OH can be obtained by a hydride reduction (e.g, $LiAlH_4$) of a 3-alkoxycarbonyl-4-aryl-1-(phenylmethyl)pyrrolidine or a 3-alkoxycarbonyl-4-arylpyrrolidine in an ethereal solvent (e.g., THF) at temperatures ranging from -10-30 °C. The 3-aryl-4-(hydroxymethyl)pyrrolidines can be selectively *N*-acylated according to standard procedures known to those skilled in the art of organic synthesis (e.g., Schotten-Baumann conditions). Specific examples of this chemistry are shown below.





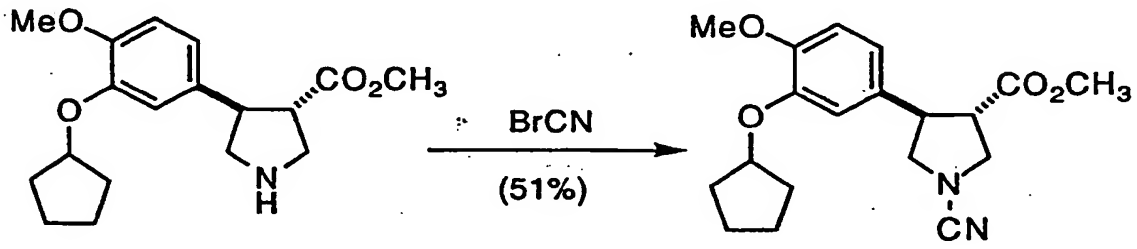
Compounds of Formula (I) in which R^3 is $CONR^6R^7$ can be obtained from the corresponding carboxylic acid. Treatment of the carboxylic acid with an activating reagent, such as 1,1'-carbonyldiimidazole (CDI), in a chlorinated solvent (e.g., CH_2Cl_2) followed by addition of an amine afforded, after purification of the amides. Specific examples of this chemistry are shown below.

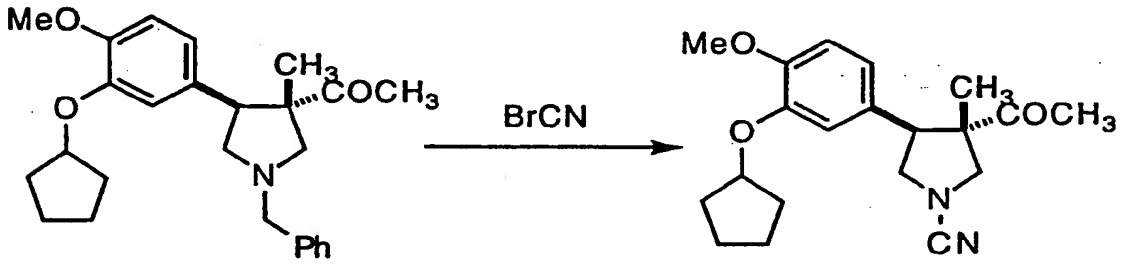




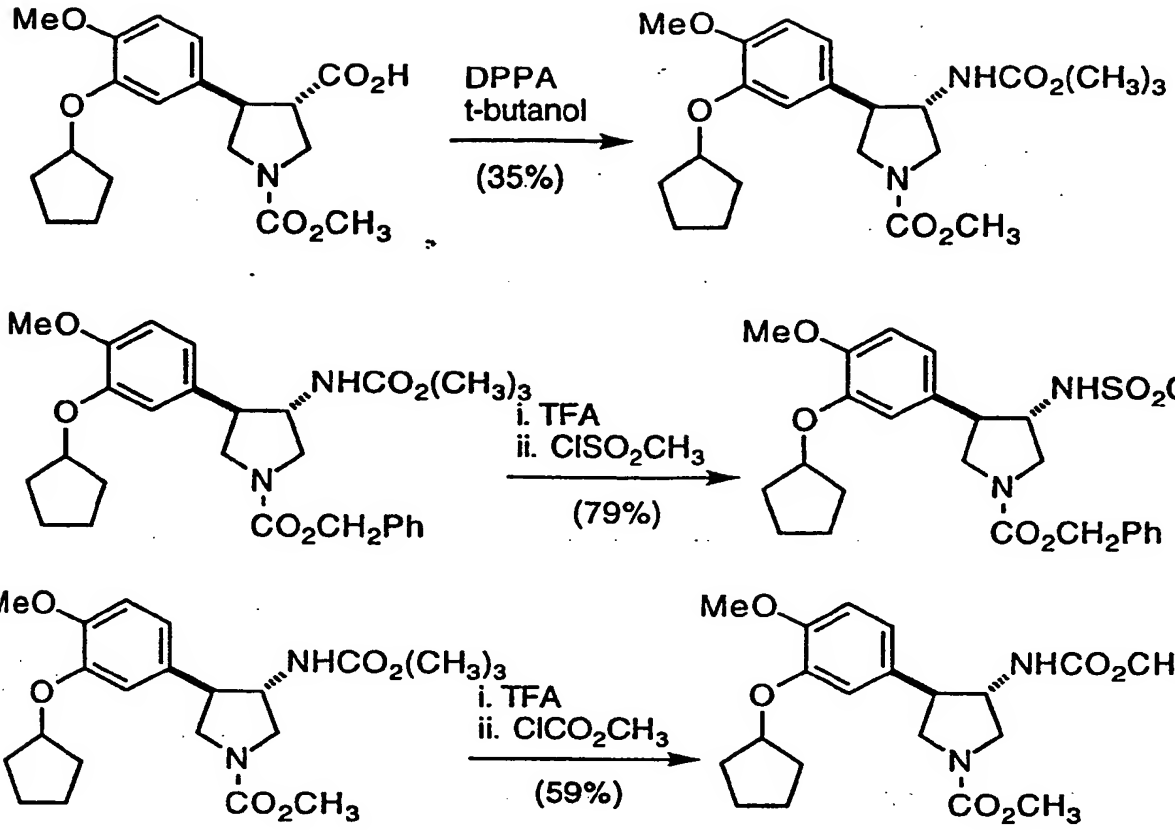
Compounds of Formula (I) where R^5 is CN are prepared by one of two methods. The free pyrrolidine can be *N*-cyanated by treatment with cyanogen bromide (BrCN) in a suitable solvent (e.g., acetonitrile) in the presence of a base. Alternatively, the *N*-phenylmethylpyrrolidine obtained directly from the azomethine ylide cycloaddition

can be treated with cyanogen bromide to affect an *N*-dealkylative cyanation reaction (von Braun reaction). These two methods are illustrated below.

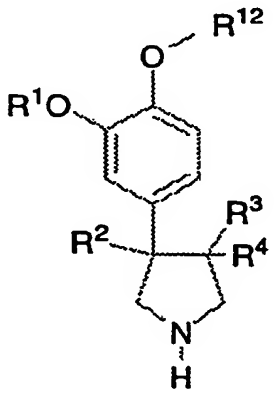




3-Amino-1-acylpyrrolidine derivatives (Formula (I) wherein R^3/R^4 is $NR^8COR^9/NR^8SO_2R^{10}$) were synthesized from the carboxylic acids by use of a Curtius rearrangement. Preferred conditions use diphenylphosphoryl azide (DPPA) in t-butanol at elevated temperature. The resulting t-butyl carbamate provides entry into the compounds of Formula (I). Solvolytic removal of the t-butyl carbamate under acidic conditions [e.g., trifluoroacetic acid (TFA)], followed by acylation of the resulting primary amine affords the compound of Formula (I). Specific examples of this chemistry are shown below.



In light of the foregoing synthesis schemes, it will be appreciated that the present invention generally contemplates a process for the preparation of a compound of Formula (I) wherein a compound of Formula (II)



(II)

with a reagent R^5-Y where Y is an appropriate leaving group. Additionally, it will be further appreciated that the present invention generally contemplates a process for the interconversion of one compound of Formula (I) to another compound of Formula (I).

GENERAL PROCEDURES

Unless otherwise noted all starting materials were obtained from commercial suppliers and used without further purification. All reactions involving oxygen- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. All reactions and chromatography fractions were analyzed by thin-layer chromatography on 250-mm silica gel plates, visualized with UV light and I_2 stain. Flash column chromatography was carried out using Merck silica gel 60 (230-400 mesh).

^{1}H-NMR spectra were measured in $CDCl_3$ using either a Varian VXZ-300 or a Varian Unity-300 instrument. *J* values are reported in Hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Apparent multiplicities are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. All mass spectra were taken in the positive ion mode under electrospray ionization (ESI), chemical ionization (CI), electron impact (EI), or by fast-atom bombardment (FAB). Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

The following section describes the preparation of intermediates that may be used in the synthesis of compounds of Formula (I).

(A). (*E*)-Methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-en-oate

To a solution of trimethylphosphonoacetate (13 mL, 82 mmol) in 36 mL of THF at 0 °C was added lithium bis(trimethylsilyl)amide (82 mL of 1M THF solution, 82 mmol). This solution was stirred for 20 min, and a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (15 g, 68 mmol) in 30 mL of THF was then added dropwise via addition funnel. When reaction was judged complete by TLC analysis, the reaction was diluted with ethyl acetate:hexanes (1:1), and the organic layer was washed with H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford (*E*)-methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-en-oate as a pale yellow solid (17.2 g, 92%). ^{1}H-NMR (300 MHz): δ 3.79 (s, 3), 3.86 (s, 3), 6.28 (d, 1, J = 16), 7.52 (d, 1, J = 16).

The following compounds were prepared according to the general procedure set forth above.

(B). (*E*)-methyl-3-[3-(3-phenoxypropoxy)-4-methoxyphenyl]-prop-2-en-oate: 100%; ^{1}H-NMR (300 MHz): δ 2.33 (q, 2, J = 6.1), 3.79 (s, 3), 3.87 (s, 3), 4.19 (t, 2, J = 6.1), 4.25 (t, 2, J = 6.1), 6.29 (d, 1, J = 16), 7.61 (d, 1, J = 16).

(C). (*E*)-1,1-Dimethylethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-en-oate

To a solution of t-butyl diethylphosphonoacetate (5.0 g, 19.8 mmol) in 15 mL of THF at 0 °C was added lithium bis(trimethylsilyl)amide (19.8 mL of 1M THF solution, 19.8 mmol). This solution was stirred for 20 min, and a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (3.64 g, 16.5 mmol) in 15 mL of THF was then added dropwise via addition funnel. After 1 hr the reaction was judged complete by TLC analysis and was diluted with ether. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oil. Silica gel chromatography (6:1:1, hexanes:ethyl acetate:CH_2Cl_2) provided an oil which was further chromatographed (8:1:1, hexanes:ethyl acetate:CH_2Cl_2) to afford (*E*)-1,1-dimethylethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-en-oate (5.0 g, 95%) as a pale yellow oil. ^{1}H-NMR (300 MHz): δ 1.52 (s, 9), 3.86 (s, 3). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.70; H, 8.25.

(D). (*E*)-1,1-Dimethylethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate

To a solution of t-butyl diethylphosphonoacetate (5.0 g, 19.8 mmol) in 40 mL of THF at -23 °C (ice:acetone) was added lithium bis(trimethylsilyl)amide (19.8 mL of 1M THF solution, 19.8 mmol). This solution was stirred for 15 min, and CH_3I (2.8 g, 21.8 mmol). After 24 hr the reaction was diluted with ether and washed successively with 1M H_3PO_4, H_2O, and brine. The solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure to an oil (5.4 g). ^{1}H-NMR analysis indicated an approximate 1:1 mixture of starting phosphonoacetate and the monomethylated derivative, which was taken on without further purification.

The phosphonoacetate mixture described above was dissolved in THF (20 mL) and cooled to 0 °C. To this solution was added lithium bis(trimethylsilyl)amide (19.8 mL of 1M THF solution, 19.8 mmol). After 15 min., a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (3.64 g, 16.5 mmol) in THF (20 mL) was then added

dropwise via addition funnel. When the reaction was judged complete by TLC analysis, the reaction mixture was diluted with ether. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to an oil (6.5 g). Silica gel chromatography (10:1, hexanes:ethyl acetate) provided (*E*)-1,1-dimethylethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate as an oil (797 mg, 12%). The remaining chromatography fractions contained product mixtures. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49 Found: C, 72.31; H, 8.56.

(E). (*E*)-Ethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate

To a solution of triethyl 2-methylphosphonopropionate (3.6 g, 15 mmol) in 30 mL of THF at 0 °C was added lithium bis(trimethylsilyl)amide (18 mL of 1M THF solution, 18 mmol). This solution was stirred for 30 min, and a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (2.75 g, 12.5 mmol) in 5 mL of THF was then added dropwise. After 4 hr the reaction was judged complete by TLC analysis and was diluted with ethyl acetate:hexanes (1:1). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (4:1, hexanes:ethyl acetate) provided (*E*)-ethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate (2.75 g, 72%) as a colorless oil that solidified on standing. ^{1}H-NMR (300 MHz): δ 1.35 (t, 3, J = 7.1), 2.14 (s, 3), 3.88 (s, 3), 4.27 (q, 2, J = 7.3), 7.62 (s, 1). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.88; H, 7.99.

(F). (*E*)-Methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate

To a solution of (*E*)-ethyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate (970 mg, 3.2 mmol) in 3 mL of 1,4-dioxane was added a solution of $LiOH \cdot H_2O$ (156 mg, 3.8 mmol) in 3 mL of H_2O. The resulting mixture was heated at 80 °C for 2 hr and 45 °C for 16 hr. The resulting solution was diluted with ether and poured into 1M H_3PO_4. The aqueous layer was extracted with ethyl acetate (2X), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Silica gel chromatography (95:5, CH_2Cl:methanol) provided (*E*)-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-enoic acid as a colorless solid (700 mg, 79%). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.39; H, 7.29.

The carboxylic acid thus obtained (610 mg, 2.2 mmol) was dissolved in 10 mL of methanol and 3 drops of con. H_2SO_4 was added. The resulting solution was heated

to reflux for 20 hr, cooled to room temperature, and partitioned between sat. $NaHCO_3$ and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2X) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oil. Silica gel chromatography (4:1, hexanes:ethyl acetate) afforded (*E*)-methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-en-oate as a colorless solid (610 mg, 96%): ^{1}H-NMR (300 MHz): d 2.15 (d, 3, J = 1.2), 3.81 (s, 3), 3.88 (s, 3), 7.63 (s, 1). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.44; H, 7.72.

(G). (*E*)-4-(3-Cyclopentoxy-4-methoxyphenyl)-3-methyl-but-3-en-2-one

To a solution of (*E*)-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-enoic acid (2.21 g, 8.0 mmol) in CH_2Cl_2 (16 mL) was added 1,1'-carbonyldiimidazole (8.8 mmol, 1.43 g). The resulting solution was stirred for 10 min and $NH(CH_3)OCH_3$•HCl (12 mmol, 1.16 g) was added. The mixture was stirred at rt for 16 hr, and triethylamine (800 mg) was added. This was stirred an additional 30 min. The solution was diluted with CH_2Cl_2 and washed successively with 1M H_3PO_4 and H_2O. The organic layers were dried (K_2CO_3), filtered and evaporated to a yellow oil. Silica gel chromatography (6:4:1, hexanes:ethyl acetate:CH_2Cl_2) provided the *N*-methyl-*N*-methoxyamide as a pale yellow oil (2.1 g, 82%). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.48; H, 7.95; N, 4.35.

The amide thus obtained (1.01 g, 3.17 mmol) was dissolved in THF (6 mL), cooled to 0 °C and treated dropwise with CH_3Li (4.0 mL of a 1.4 M ether solution). The yellow solution was stirred for 15 min, diluted with ether and washed successively with 1M H3PO4 and brine. The solution was dried (MgSO4), filtered and concentrated under reduced pressure to afford (*E*)-4-(3-cyclopentoxy-4-methoxyphenyl)-3-methyl-but-3-en-2-one as a yellow oil (832 mg, 96%). ^{1}H-NMR (300 MHz): δ 2.09 (d, 3, J = 1.2), 2.46 (s, 3), 3.89 (s, 3), 7.47 (s, 1).

(H). (*Z*)-Methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enoate

To a solution of 18-crown-6 (17 g, 64 mmol) and bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (4.5 g, 14 mmol) in 200 mL of THF was added potassium bis(trimethylsilyl)amide (31 mL of 0.5M THF solution, 15.5 mmol). After 15 min a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (2.8 g, 13 mmol) in 5 mL of THF was then added dropwise. The resulting solution was stirred at -78 °C for 30 min and quenched with sat NH_4Cl. The mixture was diluted

with ether and washed with 1M H_3PO_4, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (3:1, hexanes:ethyl acetate) provided (*Z*)-methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enoate (3.1 g, 87%), containing a trace amount of the *E*-isomer. ^{1}H-NMR (300 MHz): δ 3.74 (s, 3), 3.89 (s, 3), 5.82 (d, 1, J = 13).

(I). (*E*)-3-Cyclopentoxy-4-methoxycinnamonitrile

To a slurry of NaH (1.1 g, 27.5 mmol) in 80 mL of THF at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (4.42 g, 24.9 mmol) in 20 mL of THF. The mixture was stirred for 30 min, and a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (5.0 g, 22.7 mmol) in 20 mL of THF was then added dropwise. The mixture was for 2 hr and then diluted with ether. The mixture was washed with 1M H_3PO_4, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 3-cyclopentoxy-4-methoxycinnamonitrile (4.8 g, 87%) as a yellow oil, which was carried on without further purification. ^{1}H-NMR (300 MHz): δ 3.89 (s, 3), 5.69 (d, 1, J = 16.6).

(J). (*E*)-*N*-Methyl-*N*-methoxy-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enamide

To a solution of 3-cyclopentoxy-4-methoxybenzaldehyde (2.2 g, 10 mmol) in 15 mL of CH_2Cl_2 was added *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide (7.2 g, 20 mmol). The resulting solution was stirred for 12 hr at room temperature. Concentration under reduced pressure followed by silica gel chromatography (6:4:1, hexanes:ethyl acetate:CH_2Cl_2) provided (*E*)-*N*-methyl-*N*-methoxy-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enamide as a pale yellow oil (2.6 g, 87%). ^{1}H-NMR (300 MHz): δ 3.31 (s, 3), 3.77 (s, 3), 3.88 (s, 3).

(K). (*E*)-4-(3-Cyclopentoxy-4-methoxyphenyl)-but-3-en-2-one

To a solution of (*E*)-*N*-methoxy-*N*-methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enamide (318 mg, 1.05 mmol) in 2.5 mL of THF cooled to 0 °C was added CH_3Li (1.5 mL of 1.4 M ether solution). The resulting solution was stirred for 5 min, diluted with ether and transferred to a separatory funnel. After washing with H_2O, 1M H_3PO_4, and brine, the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (3:1, hexanes:ethyl

acetate) provided (*E*)-4-(3-cyclopentoxy-4-methoxyphenyl)-but-3-en-2-one as a white solid (234 mg, 90%). ^{1}H-NMR (300 MHz): δ 2.38 (s, 3), 3.89 (s, 3), 6.59 (d, 1, J = 16), 7.46 (d, 1, J = 16).

(L). (*E*)-5-(3-Cyclopentoxy-4-methoxyphenyl)-pent-4-en-3-one

To a solution of (*E*)-*N*-methoxy-*N*-methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enamide (1.33 g, 4.36 mmol) in 8.0 mL of THF cooled to 0 °C was added CH_3CH_2MgBr (9 mL of 1.0 M THF solution). The resulting solution was stirred for 30 min, diluted with ether and transferred to a separatory funnel. After washing with H_2O, 1M H_3PO_4, and brine, the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (4:1, hexanes:ethyl acetate) provided (*E*)-5-(3-cyclopentoxy-4-methoxyphenyl)-pent-4-en-3-one as a white solid (400 mg, 34%). ^{1}H-NMR (300 MHz): δ 1.17 (t, 3, J = 7.6), 2.69 (q, 2, J = 7.3), 3.89 (s, 3), 6.59 (d, 1, J = 16), 7.50 (d, 1, J = 16). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.52; H, 8.13.

(M). (*E*)-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-phenylprop-2-enone

To a solution of (*E*)-*N*-methoxy-*N*-methyl-3-(3-cyclopentoxy-4-methoxyphenyl)-prop-2-enamide (1.25 g, 4.0 mmol) in 10 mL of THF cooled to 0 °C was added PhLi (2.5 mL of 1.8 M ether/cyclohexane solution). The resulting solution was stirred at 0 °C for 1 hr, at which time an additional 0.5 mL of PhLi was added. After 10 min the solution was diluted with ether and treated with 5 mL of 1N HCl. After washing with H_2O and brine, the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (3:1, hexanes:ethyl acetate) provided (*E*)-3-(3-cyclopentoxy-4-methoxyphenyl)-1-phenylprop-2-enone as a yellow oil (808 mg, 62%).

(N). trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine

To a solution of *N*-methoxymethyl-*N*-(phenylmethyl)trimethylsilylmethylamine (2.84 g, 12 mmol) and (*E*)-methyl 3-(3-cyclopentoxy-4-methoxyphenyl)prop-2-enoate (2.76 g, 10 mmol) in 20 mL of CH_2Cl_2 cooled to 0 °C was added a 1 mL of a 1M solution of trifluoroacetic acid. Stirring was continued for 12 hr, and the solution was partitioned between ether and sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted ethyl acetate (2X). The combined organic layers were

dried (K_2CO_3), filtered, and concentrated under reduced pressure to a pale yellow oil. Chromatography on silica gel (3:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (3.5 g, 86%) as a colorless oil. ^{1}H-NMR (300 MHz): δ 2.74-3.09 (m, 5), 3.67 (s, 3), 3.81 (s, 3), 4.75 (m, 1).

The following compounds were prepared according to the general procedure as set forth above.

(O). cis-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine:
77%; ^{1}H-NMR (300 MHz): δ 3.2 (s, 3), 3.75 (s, 2), 3.8 (s, 3).

(P). trans-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]-1-(phenylmethyl)pyrrolidine:
98%; Anal. Calcd for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99; N, 2.95. Found: C, 73.17; H, 7.02; N, 2.99.

(Q). trans-3-methoxycarbonyl-4-(3-phenylmethoxy-4-methoxyphenyl)-1-(phenylmethyl)pyrrolidine:
46%; ^{1}H-NMR (300 MHz): δ 2.65-3.06 (m, 5), 3.63 (s, 3), 3.85 (s, 3), 5.13 (s, 2).

(R). trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-(phenylmethyl)pyrrolidine:
88%. Anal. Calcd for $C_{28}H_{37}NO_4$: C, 74.47; H, 8.26; N, 3.10. Found: C, 74.29; H, 8.33; N, 3.06.

(S). 3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-4-methyl-1-(phenylmethyl)pyrrolidine:
24%. Anal. Calcd for $C_{28}H_{37}NO_4 \cdot 0.5\ H_2O$: C, 73.39; H, 8.49; N, 2.95. Found: C, 73.36; H, 8.35; N, 2.99.

(T). trans-3-cyano-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethyl)pyrrolidine:
80%; ^{1}H-NMR (300 MHz): δ 2.77-3.18 (m, 5), 3.70 (q, 2, J = 13), 3.83 (s, 3), 6.80-7.37 (m, 8).

(U). trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-nitro-1-(phenylmethyl)pyrrolidine:
56%; ^{1}H-NMR (300 MHz): δ 3.11-3.36 (m, 3), 3.82 (s, 3), 4.75 (m, 1), 4.88 (m, 1).

(V). 3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-4-methyl-1-(phenylmethyl)pyrrolidine:
87%.

(W). 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-4-methyl-1-(phenylmethyl)pyrrolidine:
99%. Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.46; H, 7.90; N, 3.28.

(X). 3-(3-Cyclopentoxy-4-methoxyphenyl)-3-methoxycarbonyl-1-(phenylmethyl)pyrrolidine

To a solution of *N*-methoxymethyl-*N*-(phenylmethyl)trimethylsilylmethylamine (1.42 g, 6.0 mmol) and methyl 2-(3-cyclopentoxy-4-methoxyphenyl)prop-2-enoate (1.38 g, 5.0 mmol) in 10 mL of CH_2Cl_2 cooled to 0 °C was added a 0.7 mL of a 1M solution of trifluoroacetic acid. Stirring was continued for 12 hr, and the solution was partitioned between ether and sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted ethyl acetate (2X). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure to a pale yellow oil. Chromatography on silica gel (3:1, hexanes:ethyl acetate) provided 3-(3-cyclopentoxy-4-methoxyphenyl)-3-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (2.0 g, 99%) as a colorless oil. ^{1}H-NMR (300 MHz): δ 2.75 (d, 1, J = 9), 3.54 (d, 1, J = 9), 3.67 (s, 3), 3.69 (s, 2), 3.81 (s, 3). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.25; H, 7.65; N, 3.40.

(Y). trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-phenylcarbonyl-1-(phenylmethyl)pyrrolidine

To a solution of *N*-methoxymethyl-*N*-(phenylmethyl)trimethylsilylmethylamine (713 mg, 3.01 mmol) and (*E*)-3-(3-cyclopentoxy-4-methoxyphenyl)-1-phenylprop-2-enone (808 mg, 2.51 mmol) in 6 mL of CH_2Cl_2 cooled to 0 °C was added a 1 mL of a 1M solution of trifluoroacetic acid. Stirring was continued for 1 hr at 0 °C and 2 hr at room temperature. The solution was then partitioned between ether and sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted ethyl

acetate (2X). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure to a pale yellow oil. Chromatography on silica gel (3:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-phenylcarbonyl-1-(phenylmethyl)pyrrolidine (1.10 g, 96%) as a pale yellow oil. ^{1}H-NMR (300 MHz): δ 2.81-3.25 (m, 4), 3.81 (s, 3), 3.97 (m, 1), 6.73-7.80 (m, 13).

The following compounds were prepared according to the general procedure as set forth above.

(Z). trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethylcarbonyl-1-(phenylmethyl)pyrrolidine:
95%; Anal. Calcd for $C_{26}H_{33}NO_3$: C, 76.63; H, 8.16; N, 3.44. Found: C, 76.58; H, 8.17; N, 3.39.

(AA). trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methylcarbonyl-1-(phenylmethyl)pyrrolidine:
95%; ^{1}H-NMR (300 MHz): δ 2.08 (s, 3), 2.71-3.20 (m, 5), 3.65 (q, 2, J = 13), 3.82 (s, 3), 6.76-7.37 (m, 8).

(BB). trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (3.5 g, 8.6 mmol) was dissolved in 20 mL of 4% HCO_2H:methanol. While stirring at room temperature, 10% Pd/C (450 mg) was added in small portions. After several hours the reaction was diluted with methanol. Filtration through Celite followed by concentration under reduced pressure yielded a yellow oil residue. This residue was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2X). The organic layers were combined, dried (K_2CO_3), filtered, and concentrated under reduced pressure to afford a pale oil. Chromatography on silica gel (8:1:1, CH_2Cl_2:ethyl acetate:methanol) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine as a colorless oil (2.3 g, 84%). ^{1}H-NMR (300 MHz): δ 2.86-3.04 (m, 2), 3.29-3.52 (m, 4), 3.68 (s, 3), 3.83 (s, 3).

The following compounds were prepared according to the general procedure as set forth above.

(CC). trans-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine:
82%; ^{1}H-NMR (300 MHz): δ 2.31 (m, 1), 2.89-3.04 (m, 2), 3.31-3.51 (m, 4), 3.67 (s, 3), 3.83 (s, 3), 6.81-7.31 (m, 8).

(DD). 3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-4-methylpyrrolidine:
92%; ^{1}H-NMR (300 MHz): δ 0.92 (s, 3), 2.87 (d, 1, J = 11.7), 3.59 (d, 1, J = 11.7), 3.83 (s, 3), 4.20 (q, 2, J = 7.1), 6.71-6.82 (m, 3).

(EE). 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-4-methylpyrrolidine:
80%; ^{1}H-NMR (300 MHz): δ 0.93 (s, 3), 2.88 (d, 1, J = 12), 3.60 (d, 1, J = 12), 3.75 (s, 3), 3.83 (s, 3), 6.71-6.82 (m, 3).

(FF). trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-(hydroxymethyl)pyrrolidine

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (500 mg, 1.57 mmol) in 7 mL of THF at 0 °C was added $LiAlH_4$ (60 mg, 1.57 mmol). The resulting mixture was stirred for 15 min at 0°C and then allowed to stir at room temperature for 20 min. The mixture was then successively treated dropwise with H_2O (0.06 mL), 15% NaOH (0.06 mL), and H_2O (0.18 mL). The resulting suspension was then stirred for 1 hr, filtered through Celite, and concentrated under reduced pressure to an oil. Silica gel chromatography (1:1 $CHCl_3$:methanol) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(hydroxymethyl)pyrrolidine as a pale yellow oil (329 mg, 72%). ^{1}H-NMR (300 MHz): δ 2.35 (m, 1), 2.90-3.08 (m, 3), 3.30-3.76 (m, 4), 3.82 (s, 3).

(GG). trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(phenylmethyl)pyrrolidine

To a solution of trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (2.7 g, 6.6 mmol) in 27 mL of THF at 0 °C was added $LiAlH_4$ (4.0 mmol, 4 mL of 1M toluene solution). After stirring for 2 hr the reaction mixture was then successively treated dropwise with H_2O (0.15 mL), 15% NaOH (0.15 mL), and H_2O (0.46 mL). The resulting suspension was diluted with ether, stirred for 1 hr, filtered through Celite, and concentrated under reduced pressure to an oil. Silica gel chromatography (graded elution: CH_2Cl_2 then 9:1, CH_2Cl_2:methanol) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(phenylmethyl)pyrrolidine (2.0 g, 80%) as an oil.

EXAMPLES

Example 1

cis-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

cis-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (1.66 g, 4.1 mmol) was dissolved in 30 mL of 4% HCO_2H:methanol. While stirring at room temperature, 10% Pd/C (166 mg) was added in small portions. After 12 hr the reaction was diluted with methanol. Filtration through Celite followed by concentration under reduced pressure yielded a greenish oil residue, which was twice again concentrated from toluene. To this residue in 15 mL of CH_2Cl_2 at 0 °C was added 4-dimethylaminopyridine (650 mg, 5.33 mmol), followed by di-t-butyl-dicarbonate (1.07 g, 4.92 mmol). The bath was removed, and the mixture was stirred at room temperature. After 45 min the reaction mixture was diluted with CH_2Cl_2, washed with 1M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (2:1, hexanes:ethyl acetate) provided cis-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine as a colorless oil (1.1 g, 64%), m.p. 85-87 °C. ^{1}H-NMR (300 MHz): δ 1.50 (s, 9), 3.44 (s, 3), 3.82 (s, 3), 4.72 (bs, 1). Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.93; H, 7.95; N, 3.32.

The following compounds were prepared according to the general procedure set forth above in Example 1:

Example 2

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

38%; ^{1}H-NMR (300 MHz): δ 1.48 (s, 9), 3.64 (s, 3), 3.83 (s, 3), 4.76 (bs, 1). Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.73; H, 7.93; N, 3.29.

Example 3

trans-3-methoxycarbonyl-1-(1,1-dimethylethoxycarbonyl)-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine

(R^1 = phenoxypropyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

42%; Anal. Calcd for $C_{27}H_{35}NO_7$: C, 66.79; H, 7.27; N, 2.89. Found: C, 66.63; H, 7.33; N, 2.80.

Example 4

trans-3-(3,4-dimethoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = methyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

71%; Anal. Calcd. for $C_{19}H_{27}NO_6$:C, 62.45; H, 7.45; N, 3.83. Found: C, 62.24; H, 7.48; N. 3.81.

Example 5

3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-3-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = $-CO_2CH_3$; R^3 = H; R^4 = H ; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

3-(3-Cyclopentoxy-4-methoxyphenyl)-3-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (1.6 g, 3.9 mmol) was dissolved in 40 mL of 4% HCO_2H:methanol. While stirring at room temperature, 10% Pd/C (160 mg) was added in small portions. After 12 hr the reaction was diluted with methanol. Filtration through Celite followed by concentration under reduced pressure yielded a greenish oil residue, which was twice again concentrated from toluene. To this residue in 10 mL of CH_2Cl_2 at 0 °C was added 4-dimethylaminopyridine (620 mg, 5.0 mmol), followed by di-t-butyl-dicarbonate (1.02 g, 4.7 mmol). The bath was removed, and the mixture was stirred at room temperature. After 3 hr the reaction mixture was

diluted with CH_2Cl_2, washed with 1M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (5:1, hexanes:ethyl acetate) provided 3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-3-(methoxycarbonyl)pyrrolidine as a colorless oil (1.2 g, 70%). ^{1}H-NMR indicates a 1:1 mixture of rotamers. Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.66; H, 8.01; N, 3.26.

Example 6

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(hydroxymethyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = CH_2OH; R^4 = H ; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(phenylmethyl)pyrrolidine (200 mg, 0.53 mmol) was dissolved in 5 mL of 4% HCO_2H:methanol. While stirring at room temperature, 10% Pd/C (30 mg) was added. After 4 hr the reaction was diluted with methanol. Filtration through Celite followed by concentration under reduced pressure yielded an oil residue. To this residue dissolved in 2 mL of CH_2Cl_2 at 0 °C was added 4-dimethylaminopyridine (64 mg, 0.5 mmol), followed by di-t-butyl-dicarbonate (126 mg, 0.58 mmol). The bath was removed, and the mixture was stirred at room temperature for 15 hr. The reaction mixture was then diluted with CH_2Cl_2, washed with 1M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (1:1, hexanes:ethyl acetate) provided 3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(hydroxymethyl)pyrrolidine as a colorless oil (130 mg, 63%). Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.49; N, 3.58. Found: C, 67.23; H, 8.58; N, 3.49.

Example 7

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = CH_2OH; R^4 = H ; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a vigorously stirring mixture of 3-(3-cyclopentoxy-4-methoxyphenyl)-4-(hydroxymethyl)pyrrolidine (328 mg, 1.13 mmol) in 4 mL of 1:1 ethyl acetate:sat aq

$NaHCO_3$ was added methyl chloroformate (138 mg, 1.47 mmol). When TLC analysis indicated a complete reaction the mixture was diluted with ethyl acetate, and the layers were separated. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure to provide 3-(3-cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(methoxycarbonyl)pyrrolidine as a colorless viscous oil (273 mg, 69%). Anal: Calcd for $C_{19}H_{27}NO_5 \cdot 0.5\ H_2O$: C, 63.67; H, 7.87; N, 3.91. Found: C, 63.30; H, 7.75; N, 3.92.

Example 8

trans-1-Aminocarbonyl-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CONH_2$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine (419 mg, 1.0 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added 2.3 mL of trifluoroacetic acid. The solution was stirred for 12 hr at room temperature, and concentrated to an oil. The oil was dissolved in 2 mL of CH_2Cl_2 and 4-dimethylaminopyridine 366 mg, 3.0 mmol) was added. To this solution at 0 °C was added trimethylsilylisocyanate (1.15 g, 10.0 mmol). The bath was removed and the resulting mixture was allowed to stir for 60 hr. After dilution with CH_2Cl_2, the reaction mixture was washed with 1M H_3PO_4 and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (9:1, CH_2Cl_2:methanol) provided a foam. Crystallization with diisopropyl ether afforded trans-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine as a white solid (243 mg, 67%), m.p. 127-129 °C. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 63.07; H, 7.20; N, 7.76.

The following compounds were prepared according to the general procedure set forth above in Example 8:

Example 9

cis-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CONH_2$; R^{12} = methyl)

81%; m.p. 133-35 °C. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.82; H, 7.27; N, 7.71.

Example 10

1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-3-(methoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = $-CO_2CH_3$; R^3 = H; R^4 = H ; R^5 = $-CONH_2$; R^{12} = methyl)

95%: ^{1}H-NMR (300 MHz): δ 2.94 (m, 1), 3.38-3.59 (m, 2), 3.67 (s, 3), 3.84 (s, 3), 6.83 (s, 3). Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.87; H, 7.27; N, 7.66.

Example 11

trans-1-Methoxycarbonyl-3-methoxycarbonyl-4-(3-phenylmethoxy-4-methoxyphenyl)pyrrolidine

(R^1 = $-CH_2$-(phenyl); R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H ; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of 3-methoxycarbonyl-4-[3-(3-phenylmethoxy)-4-methoxyphenyl]-1-(phenylmethyl)pyrrolidine (3.0 g, 6.95 mmol) in 14 mL of CH_3CN was added methyl chloroformate (1.31 g, 13.9 mmol). The resulting solution was heated to reflux. After 1.5 hr an additional 650 mg of methyl chloroformate was added. After 4 hr the solution was concentrated. Silica gel chromatography of the residue (2:1, hexanes:ethyl acetate) yielded trans-1-methoxycarbonyl-3-methoxycarbonyl-4-(3-phenylmethoxy-4-methoxyphenyl)pyrrolidine as a cloudy, colorless oil (2.61 g, 94%). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.92; H, 6.38; N, 3.41.

Example 12

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-methyl-4-(methycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $COCH_3$; R^4 = $-CH_3$; - R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of (E)-3-(3-cyclopentoxy-4-methoxyphenyl)-2-methyl-prop-2-enoic acid (2.21 g, 8.0 mmol) in CH_2Cl_2 (16 mL) was added 1,1'-carbonyldiimidazole (8.8 mmol, 1.43 g). The resulting solution was stirred for 10 min and $NH(CH_3)OCH_3$•HCl (12 mmol, 1.16 g) was added. The mixture was stirred at rt for 16 hr, and triethylamine (800 mg) was added. This was stirred an additional 30 min. The solution was diluted with CH_2Cl_2 and washed successively with 1M H_3PO_4 and H_2O. The organic layers were dried (K_2CO_3), filtered, and evaporated to a yellow oil. Silica gel chromatography (6:4:1, hexanes:ethyl acetate:CH_2Cl_2) provided the N-methyl-N-methoxyamide as a pale yellow oil (2.1 g, 82%).

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.48; H, 7.95; N, 4.35.

The amide thus obtained (1.01 g, 3.17 mmol) was dissolved in THF (6 mL), cooled to 0 °C, and treated dropwise with CH_3Li (4.0 mL of a 1.4 M ether solution). The yellow solution was stirred for 15 min, diluted with ether, and washed successively with 1M H_3PO_4 and brine. The solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford (E)-4-(3-cyclopentoxy-4-methoxyphenyl)-3-methyl-but-3-en-2-one as a yellow oil (832 mg, 96%).

^{1}H-NMR (300 MHz): d 2.09 (d, 3, J = 1.2), 2.46 (s, 3), 3.89 (s, 3), 7.47 (s, 1).

To a solution of N-methoxymethyl-N-(phenylmethyl)trimethylsilylmethylamine (1.44 g, 6.08 mmol) and (E)-4-(3-cyclopentoxy-4-methoxyphenyl)-3-methyl-but-3-en-2-one (832 mg, 3.04 mmol) in 6 mL of CH_2Cl_2 cooled to 0 °C was added a 0.6 mL of a 1M solution of trifluoroacetic acid. Stirring was continued for 2 days at room temperature, at which time an additional 0.7 g of N-methoxymethyl-N-(phenylmethyl)trimethylsilylmethylamine was added. The solution was brought to reflux and maintained at that temperature for 4 hr. The solution was cooled to rt, and partitioned between ether and sat. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate (2X). The combined organic layers were dried (K_2CO_3), filtered, and concentrated under reduced pressure to a pale yellow oil. Chromatography on silica gel (95:5 dichloromethane:ether) provided (±)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(phenylmethyl)pyrrolidine (714 mg, 58%) as a colorless oil.

^{1}H-NMR (300 MHz): d 0.83 (s, 3), 1.57-1.96 (m, 8), 2.24 (s, 3), 2.42 (d, 1, J = 9.8), 2.81-3.09 (m, 2), 3.14 (d, 1, J = 9.6), 3.59-3.85 (m, 3), 3.82 (s, 3), 4.73-4.76 (m, 1), 6.71-6.82 (m, 3), 6.88 (s, 1), 7.24-7.40 (m, 5).

To a solution of (±)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(phenylmethyl)pyrrolidine (316 mg, 0.78 mmol) in 3 mL of CH_3CN was added methyl chloroformate (370 mg, 3.9 mmol). The resulting solution was heated at 80 °C for 2 hr and then maintained at 50 °C for an additional 14 hr. The solution was then cooled to rt and concentrated under reduced pressure to a yellow oil. Silica gel chromatography (2:1, hexanes:ethyl acetate) provided (±)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(methoxycarbonyl)pyrrolidine as a colorless oil, which solidified on standing (187 mg, 64%).

^{1}H-NMR (300 MHz, mixture of rotamers, diagnostic peaks only): d 1.02 and 1.03 (s, 3), 2.15 and 2.17 (s, 3), 3.29 and 3.38 (d, 1, J = 11.0), 3.75 (s, 3), 3.84 (s, 3), 4.73 (bs, 1), 6.67-6.82 (m, 3). Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.00; H, 7.78; N, 3.66.

The following compounds were prepared according to the general procedure set forth above in Example 11:

Example 13

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-(methoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2C(CH_3)_3$; R^4 = H ; R^5 = $-CO_2CH_3$; R^{12} = methyl)

80%; Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.73; H, 8.03; N, 3.27.

Example 14

3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-methoxycarbonyl-4-methylpyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2C(CH_3)_3$; R^4 = $-CH_3$; R^5 = $-CO_2CH_3$; R^{12} = methyl)

79%; Anal. Calcd for $C_{24}H_{35}NO_6 \cdot 0.5\ H_2O$: C, 65.14; H, 8.20; N, 3.17. Found: C, 65.11; H, 8.00; N, 3.13.

Example 15

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethylcarbonyl-1-(methoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-COCH_2CH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

67%; Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.14; H, 7.86; N, 3.73.

Example 16

trans-1-methoxycarbonyl-3-nitro-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine:

26%: Anal. Calcd for $C_{22}H_{26}N_2O_7$: C, 61.39; H, 6.09; N, 6.51. Found: C, 61.23; H, 6.16; N, 6.43.

(R^1 = phenoxypropyl; R^2 = H; R^3 = $-NO_2$; R^4 = H, R^5 = $-CO_2CH_3$; R^{12} = methyl)

Example 17

trans-3-Cyano-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -CN; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of 3-cyano-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethyl)pyrrolidine (300 mg, 0.79 mmol) in 2 mL of CH_3CN in a thick-walled glass sealable tube was added methyl chloroformate (300 mg, 3.19 mmol). The tube was sealed and the resulting solution was heated to 80 °C for 12 hr. After cooling to room temperature, the solution was concentrated. Silica gel chromatography of the residue (2:1, hexanes:ethyl acetate) provided trans-3-cyano-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine as a white solid (233 mg, 85%), m.p. 101-104 °C. Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.14; H, 7.06; N, 8.10.

The following compound was prepared according to the general procedure set forth above in Example 17:

Example 18

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-nitropyrrolidine:
(R^1 = cyclopentyl; R^2 = H; R^3 = $-NO_2$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

^{1}H-NMR (300 MHz): δ 3.76 (s, 3), 3.82 (s, 3), 4.73 (m, 1), 4.93 (m, 1). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.68; N, 7.69. Found: C, 59.28; H, 6.66; N, 7.62.

Example 19

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylcarbonyl)pyrrolidine
(R^1 = cyclopentyl; R^2 = H; R^3 = $-COCH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methylcarbonyl-1-(phenylmethyl)pyrrolidine (703 mg, 1.78 mmol) in 3.5 mL of dichloroethane in a thick-walled glass sealable tube was added methyl chloroformate (336 mg, 3.56 mmol). The tube was sealed and the resulting solution was heated to 80 °C for 8 hr. After cooling to room temperature, the solution was concentrated. Silica gel chromatography of the residue (6:3:1, hexanes:ethyl acetate:CH_2Cl_2) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylcarbonyl)pyrrolidine as a viscous oil (350 mg, 54%). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.24; H, 7.60; N, 3.79.

The following compound was prepared according to the general procedure set forth above in Example 19:

Example 20

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(phenylcarbonyl)pyrrolidine:
(R^1 = cyclopentyl; R^2 = H; R^3 = phenylcarbonyl; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

59%; Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.72; H, 6.95; N, 3.25.

Example 21

trans-1-Methoxycarbonyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine

(R^1 = phenoxypropyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of 3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine (720 mg, 1.87 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added DMAP (275 mg, 2.25 mmol), followed by methyl chloroformate (213 mg, 2.25 mmol). The solution was stirred for 2 hr, diluted with ether, and washed with 1M H_3PO_4. The aqueous layer was extracted with ether (2X) and ethyl acetate (1X). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to a colorless oil. Silica gel chromatography (4:2:1, hexanes:ethyl acetate:CH_2Cl_2) provided trans-1-methoxycarbonyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine as a colorless oil (634 mg, 77%). Anal. Calcd for $C_{24}H_{29}NO_7$: C, 64.99; H, 6.59; N, 3.16. Found: C, 64.85; H, 6.57; N, 3.15.

The following compounds were prepared according to the general procedure set forth above in Example 21:

Example 22

3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-methoxycarbonyl-4-methylpyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_2CH_3$; R^4 = $-CH_3$; R^5 = $-CO_2CH_3$; R^{12} = methyl)

85%; Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.19; H, 7.71; N, 3.35

Example 23

3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-methoxycarbonyl-4-methylpyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_2CH_3$; R^4 = $-CH_3$; R^5 = $-CO_2CH_3$; R^{12} = methyl)

75%; Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 63.64; H, 7.48; N, 3.54.

Example 24

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

96%; ^{1}H-NMR (300 MHz): δ 3.65 (s, 3), 3.73 (s, 3), 3.82 (s, 3).

Example 25

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylcarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-COCH_3$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (605 mg, 1.89 mmol) in 5 mL of CH_2Cl_2 was added 4-dimethylaminopyridine (347 mg, 2.84 mmol), followed by 1 mL of acetic anhydride After 12 hr the reaction was diluted with CH_2Cl_2 and washed with 1M H_3PO_4. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (2:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylcarbonyl)pyrrolidine as a viscous oil (370 mg, 54%). ^{1}H-NMR (300 MHz) analysis indicates a 1:1 mixture of amide rotamers (δ 2.07 and 2.09 singlets). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.19; H, 7.58; N, 3.82.

Example 26

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-COCH_2CH_3$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (300 mg, 0.94 mmol) in 3 mL of CH_2Cl_2 at 0 °C was added 4-dimethylaminopyridine (149 mg, 1.22 mmol), followed by propionic anhydride (135 mg, 1.03 mmol). After 5 hr the reaction was diluted with CH_2Cl_2 and washed with 1M H_3PO_4. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (1:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-(methoxycarbonyl)pyrrolidine as a viscous oil (197 mg, 56%). Anal. Calcd for $C_{21}H_{29}NO_5 \cdot 0.25\ H_2O$: C, 66.38; H, 7.83; N, 3.69. Found: C, 66.48; H, 7.87; N, 3.65.

Example 27

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(1-imidazolylcarbonyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = imidazolylcarbonyl; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (400 mg, 1.25 mmol) in 3 mL of CH_2Cl_2 cooled to 0 °C was added 1,1'-carbonyldiimidazole (223 mg, 1.38 mmol). After 30 min the reaction was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography of the foamy solid (9:1, CH_2Cl_2:methanol) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-imidazolylcarbonyl-4-(methoxycarbonyl)pyrrolidine as a white solid (504 mg, 97%), m.p. 40-45 °C. Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 63.11; H, 6.60; N, 10.09.

Example 28

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-formyl-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = -CHO; R^{12} = methyl)

A solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (620 mg, 1.94 mmol) in 5 mL of ethyl formate was

heated at reflux for 3 hr. The reaction was diluted with ether and concentrated. The residue was dissolved in ether and washed with 1M H_3PO_4. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (2:1, ethyl acetate:hexanes) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-formyl-4-(methoxycarbonyl)pyrrolidine as a colorless oil (567 mg, 84%). ^{1}H-NMR (300 MHz): δ 3.11-3.21 (1, m), 3.65 (s, 3), 3.82 (s, 3), 6.73-6.82 (m, 3), 8.26 (s, 1).

The following compound was prepared according to the general procedure set forth above in Example 28:

Example 29

trans-1-formyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine:

(R^1 = phenoxypropyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = -CHO; R^{12} = methyl)

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.72; H, 6.59; N, 3.41.

Example 30

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(1-methylethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH(CH_3)_2$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of trans-3-carboxy-4-[(3-cyclopentoxy-4-methoxy)phenyl]-1-(methoxycarbonyl)pyrrolidine (200 mg, 0.55 mmol) in 3 mL of 2-propanol was added 2 drops of concentrated H_2SO_4, and the solution was heated to reflux for 36 hr. The solution was cooled to room temperature, diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. Silica gel chromatography (3:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylethoxycarbonyl)pyrrolidine as a viscous, pale yellow oil (126 mg, 56%). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 64.89; H, 7.73; N, 3.38.

Example 31

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_2CH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of trans-3-carboxy-4-[(3-cyclopentoxy-4-methoxy)phenyl]-1-(methoxycarbonyl)pyrrolidine (300 mg, 0.83 mmol) in 5 mL of ethanol was added 2 drops of concentrated H_2SO_4, and the solution was heated to reflux for 3 hr. The solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. Silica gel chromatography (2:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-(methoxycarbonyl)pyrrolidine as a pale yellow oil (200 mg, 62%). Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.37; H, 7.51; N, 3.52.

Example 32

trans-3-Carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = - $CO_2C(CH_3)_3$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine (680 mg, 1.63 mmol) in 2 mL of 1,4-dioxane at 0 °C was added $LiOH•H_2O$ (82 mg, 1.96 mmol) dissolved in 5 mL of H_2O. Stirring was continued at 0 °C for 1 hr, at which time the resulting solution was diluted with ether and poured into 1M H_3PO_4. The aqueous layer was extracted with ether (3X), washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give trans-3-carboxy-4-[(3-cyclopentoxy-4-methoxy)phenyl]-1-(1,1-dimethylethoxycarbonyl)pyrrolidine, which solidified to a colorless foamy solid under high vacuum (640 mg, 94%). Anal. Calcd for $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.11; H, 7.87; N, 3.28.

The following compounds were prepared according to the general procedure set forth above in Example 32:

Example 33

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

83%; ^{1}H-NMR (300 MHz): δ 3.13 (m, 1), 3.72 (s, 3), 3.82 (s, 3), 6.76-6.83 (m, 3).

Example 34

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = $-CO_2CH_2$-phenyl; R^{12} = methyl)

91%; Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.04; H, 6.79; N, 3.01.

Example 35

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-methylethoxycarbonyl)pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = $-CO_2CH(CH_3)_2$; R^{12} = methyl)

80%; ^{1}H-NMR (300MHz): δ 1.26 (bs, 6), 3.82 (s, 3), 4.94 (m, 1), 6.73-6.83 (m, 3).

Example 36

trans-3-carboxy-1-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine:

(R^1 = phenoxypropyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

89%; Anal. Calcd for $C_{23}H_{27}NO_7 \cdot 0.25\ H_2O$: C, 63.66; H, 6.39; N, 3.23. Found: C, 63.77; H, 6.65; N, 3.21.

Example 37

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-formylpyrrolidine:
(R^1 = cyclopentyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = -CHO; R^{12} = methyl)

Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.76; H, 6.93; N, 4.09.

Example 38

trans-1-aminocarbonyl-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)pyrrolidine:
(R^1 = cyclopentyl; R^2 = H; R^3 = -COOH; R^4 = H; R^5 = -$CONH_2$; R^{12} = methyl)

68%; m.p. 199-209 °C.

Example 39

trans-3-Aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine
(R^1 = cyclopentyl; R^2 = H; R^3 = -$CONH_2$; R^4 = H; R^5 = -CO_2CH_3 ; R^{12} = methyl)

To a solution of trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine (1.5 g, 4.1 mmol) in 11 mL of CH_2Cl_2 at 0 °C was added 1,1'-carbonyldiimidazole (736 mg, 4.5 mmol) in portions. The cooling bath was removed, and the solution was stirred at room temperature for 20 min. Ammonia gas was passed over the stirring solution for 4 min, and stirring was continued an additional 15 min. The solution was diluted with CH_2Cl_2 and poured into 1M H_3PO_4. The aqueous layer was extracted with CH_2Cl_2 (2X), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale yellow foam. Silica gel chromatography (8:1:1, CH_2Cl_2:ethyl acetate:methanol) provided trans-3-aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine as a white solid (1.1 g, 76%), m.p. 130-32 °C. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 63.03; H, 7.28; N, 7.65.

Example 40

trans-3-Aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CONH_2$; R^4 = H; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

To a solution of trans-3-carboxy-4-[(3-cyclopentoxy-4-methoxy)phenyl]-1-(1,1-dimethylethoxycarbonyl)pyrrolidine (400 mg, 0.98 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added 1,1'-carbonyldiimidazole (154 mg, 1.0 mmol). The solution was stirred for 20 min. Ammonia gas was then passed over the stirring solution for 3 min, and stirring was continued an additional 30 min. The solution was diluted with CH_2Cl_2 and poured into 1M H_3PO_4. The aqueous layer was extracted with CH_2Cl_2 (2X), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale yellow foam. Silica gel chromatography (9:1, CH_2Cl_2:methanol) provided trans-3-aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine as a tacky white solid (275 mg, 74%). Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.33; H, 7.97; N, 6.93. Found: C, 65.07; H, 8.07; N, 6.85.

Example 41

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-[(*N*-phenylmethyl)aminocarbonyl]pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CONHCH_2$-(phenyl)
R^4 = H; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

To a solution of trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine (300 mg, 0.75 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added 1,1'-carbonyldiimidazole (120 mg, 0.75 mmol). The cooling bath was removed, and the solution was stirred at room temperature for 30 min. Benzylamine (150 mg, 1.5 mmol) was added and stirring was continued for 1 hr. The solution was diluted with ether and poured into 1M H_3PO_4. The aqueous layer was extracted with CH_2Cl_2 (2X), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale yellow foam. Silica gel chromatography (1:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-[(*N*-phenylmethyl)aminocarbonyl]pyrrolidine as a tacky white solid (275 mg, 74%). Anal. Calcd for $C_{29}H_{38}N_2O_5$: C, 70.42; H, 7.74; N, 5.66. Found: C, 70.42; H, 7.80; N, 5.67.

Example 42

trans-3-[(3-Cyclopentoxy-4-methoxy)phenyl]-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine
(R^1 = cyclopentyl; R^2 = H; R^3 = $-NHCO_2C(CH_3)_3$
R^4 = H; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

A solution of trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine (1.00 g, 2.47 mmol), triethylamine (274 mg, 2.72 mmol), and diphenylphosphoryl azide (744 mg, 2.72 mmol) in 10 mL of t-butanol was heated to 90 °C for 12 hr. The resulting solution was concentrated, and the residue was partitioned between ether and 1M H_3PO_4. The organic layer was washed with 2N NaOH and brine, dried over $MgSO_4$, filtered, and concentrated to a colorless foam. Silica gel chromatography (5:2, hexanes:ethyl acetate) provided trans-3-[(3-cyclopentoxy-4-methoxy)phenyl]-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine as a white solid (658 mg, 56%): m.p. 65-69 °C. Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.34; H, 8.43; N, 5.98.

The following compounds were prepared according to the general procedure set forth above in Example 42:

Example 43

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(methoxycarbonyl)pyrrolidine:
(R^1 = cyclopentyl; R^2 = H; R^3 = $-NHCO_2C(CH_3)_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

35%; Anal. Calcd for $C_{23}H_{34}N_2O_6$: C, 63.58; H, 7.89; N, 6.45. Found: C, 63.35; H, 7.91; N, 6.40.

Example 44

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine:
(R^1 = cyclopentyl; R^2 = H; R^3 = $-NHCO_2C(CH_3)_3$; R^4 = H; R^5 = $-CO_2CH_2$-phenyl; R^{12} = methyl)

41%; Anal. Calcd for $C_{29}H_{38}N_2O_6$: C, 68.21; H, 7.50; N, 5.49. Found: C, 67.96; H, 7.44; N, 5.63.

Example 45

trans-3-[(3-Cyclopentoxy-4-methoxy)phenyl]-4-[*N*-(1,1-dimethylethoxycarbonyl)-*N*-methyl]-1-(phenylmethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-N(CH_3)CO_2C(CH_3)_3$; R^4 = H; R^5 = $-CO_2CH_2$-phenyl; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine (200 mg, 0.39 mmol) in 3 mL of DMF was added sodium bis(trimethylsilyl)amide (0.43 mL, 0.43 mmol). After 5 min methyl iodide (111 mg, 0.78 mmol) was added. The reaction mixture was stirred until TLC analysis indicated complete reaction. The reaction was diluted with ether and washed with 1M H_3PO_4 and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (2:1, hexanes:ethyl acetate), performed twice, provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-[*N*-(1,1-dimethylethoxycarbonyl)-N-methyl]-1-(phenylmethoxycarbonyl)pyrrolidine as a white solid (110 mg, 54%), m.p. 44-47 °C. Anal. Calcd for $C_{30}H_{40}N_2O_6$: C, 68.68; H, 7.68; N, 5.34. Found: C, 68.55; H, 7.69; N, 5.35.

Example 46

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-*N*-(methylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-NHSO_2CH_3$; R^4 = H; R^5 = $-CO_2CH_2$-phenyl; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine (130 mg, 0.26 mmol) in 0.5 mL of CH_2Cl_2 was added 0.5 mL of trifluoroacetic acid. When the reaction was judged complete by TLC analysis, the reaction was diluted with CH_2Cl_2 and treated with 2N NaOH. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure to an oil. This oil was dissolved in 1 mL of CH_2Cl_2 and treated with triethylamine (103 mg, 1.01 mmol), followed by methanesulfonyl chloride

(40 mg, 0.31 mmol). The solution was stirred for 12 hr, diluted with ethyl acetate, washed with 1M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (9:1, CH_2Cl_2:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(methylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine as a foamy white solid (98 mg, 79%). Anal. Calcd for $C_{25}H_{32}N_2O_6S$: C, 61.46; H, 6.60; N, 5.73. Found: C, 61.56; H, 6.68; N, 5.78.

Example 47

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)-4-*N*-(trifluoromethylsulfonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$NHSO_2CF_3$; R^4 = H; R^5 = -CO_2CH_2-phenyl; R^{12} = methyl)

To a solution of trans-3-[(3-cyclopentoxy-4-methoxy)phenyl]-4-N-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine (201 mg, 0.39 mmol) in 0.5 mL of CH_2Cl_2 at 0 °C was added 1.5 mL of trifluoroacetic acid. When the reaction was judged complete by TLC analysis, the reaction was diluted with CH_2Cl_2 and treated with 2N NaOH. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure to an oil. This oil was dissolved in 1.5 mL of CH_2Cl_2 and treated with triethylamine (159 mg, 1.58 mmol), followed by trifluoromethanesulfonic anhydride (134 mg, 0.47 mmol). The solution was stirred for 4 hr, diluted with ethyl acetate, washed successively with 1M H_3PO_4, sat $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (3:1:1, hexanes:CH_2Cl_2:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)-4-*N*-(trifluoromethylsulfonyl)pyrrolidine as a foamy white solid (75 mg, 35%). Anal. Calcd for $C_{25}H_{29}F_3N_2O_6S$: C, 55.34; H, 5.39; N, 5.16. Found: C, 55.31; H, 5.71; N, 4.74.

Example 48

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-*N*-(phenylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$NHSO_2$-phenyl; R^4 = H; R^5 = -CO_2CH_2-phenyl; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine (130 mg, 0.26 mmol) in 0.5 mL of CH_2Cl_2 was added 0.5 mL of trifluoroacetic acid. When the reaction was judged complete by TLC analysis, the reaction was diluted with CH_2Cl_2 and treated with 2N NaOH. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure to an oil. This oil was dissolved in 1 mL of CH_2Cl_2 and treated with triethylamine (103 mg, 1.01 mmol), followed by phenylsulfonyl chloride (54 mg, 0.31 mmol). The solution was stirred for 12 hr, diluted with ethyl acetate, washed with 1M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (9:1, CH_2Cl_2:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(methylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine as a foamy white solid (121 mg, 86%). Anal. Calcd for $C_{30}H_{34}N_2O_6S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.57; H, 6.30; N, 5.04.

Example 49

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-*N*-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-NHCO_2CH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine (200 mg, 0.42 mmol) in 0.5 mL of CH_2Cl_2 was added 1.5 mL of trifluoroacetic acid. When the reaction was judged complete by TLC analysis, the reaction was diluted with CH_2Cl_2 and treated with 2N NaOH. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure to an oil. This oil was dissolved in 3 mL of CH_2Cl_2, cooled to 0 °C and treated with DMAP (112 mg, 0.92 mmol), followed by methyl chloroformate (217 mg, 2.31 mmol). The solution was stirred for 2 hr, diluted with ethyl acetate, washed with 1M H_3PO_4, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (9:1, CH_2Cl_2:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-*N*-(methoxycarbonyl)pyrrolidine as a foamy white solid (100 mg). Anal. Calcd for $C_{20}H_{28}N_2O_6 \cdot 0.25\ H_2O$: C, 60.52; H, 7.24; N, 7.06. Found: C, 60.37; H, 7.28; N, 6.97.

Example 50

trans-1-Aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-NHCO_2C(CH_3)_3$; R^4 = H; R^5 = $-CONH_2$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine (116 mg, 0.23 mmol) in 3 mL of 4% HCO_2H:methanol was added 10% Pd-C (13 mg). A balloon of H_2 gas was then attached and the reaction suspension was stirred at room temperature under an atmosphere of H_2.When the reaction was judged complete by TLC analysis, the reaction was diluted with methanol and filtered through a plug of Celite. Concentation under reduced pressure led to an off-white solid, which was partitioned between CH_2Cl_2 and sat. $NaHCO_3$. The organic layer was dried over K_2CO_3, filtered and concentrated under reduced pressure. The resulting product was dissolved in 1 mL of CH_2Cl_2 and treated at 0 °C with DMAP (85 mg) and trimethylsilyl isocyanate (280 mg). The solution was stirred for 72 hr, diluted with CH_2Cl_2, washed successively with 1M H_3PO_4, sat $NaHCO_3$, and brine. The organic layer was dried over K_2CO_3, filtered, and concentrated under reduced pressure. Silica gel chromatography (9:1, CH_2Cl_2:methanol) provided trans-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)pyrrolidine as a white solid (57 mg, 60%). Anal. Calcd for $C_{22}H_{33}N_3O_5$: C, 62.99; H, 7.93; N, 10.02. Found: C, 62.81; H, 7.95; N, 9.97.

Example 51

trans-1-Aminothiocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-CSNH_2$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (250 mg, 0.78 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added DMAP (286 mg, 2.34 mmol), followed by trimethylsilyl isothiocyanate (1.09 mL, 7.8 mmol). The solution was stirred for 72 hr, diluted with CH_2Cl_2, and washed with 1M H_3PO_4. The aqueous layer was extracted with CH_2Cl_2 (2X). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to a colorless oil. Silica gel chromatography (9:1, CH_2Cl_2:methanol), followed again by silica gel chromatography (1:1, hexanes:ethyl acetate) provided trans-1-aminothiacarbonyl-3-

(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine as a foamy white solid (215 mg, 73%). Anal. Calcd for $C_{19}H_{26}N_2O_4S$: C, 60.29; H, 6.92; N, 7.40. Found: C, 60.31; H, 6.95; N, 7.34.

Example 52

trans-1-Cyano-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = -CN; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (300 mg, 0.94 mmol) and K_2CO_3 (195 mg, 1.5 mmol) in 5 mL of CH_3CN at 0 °C was added cyanogen bromide (120 mg, 1.13 mmol). The solution was stirred for 24 hr, diluted with H_2O and ethyl acetate, and washed with brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to an oil. Silica gel chromatography (3:1, hexanes:ethyl acetate) provided trans-1-cyano-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine as a white solid (166 mg, 51%).m.p. 78-80 °C. Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.30; H, 7.04; N, 8.15.

Example 53

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-CO_2CH_2$-phenyl; R^{12} = methyl)

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethyl)pyrrolidine (3.1 g, 7.5 mmol) was dissolved in 50 mL of 4% HCO_2H:methanol. While stirring at room temperature, 10% Pd/C (400 mg) was added in small portions. After 16 hrs the reaction was diluted with methanol. Filtration through Celite followed by concentration under reduced pressure yielded a yellow oil residue. This residue was dissolved in CH_2Cl_2 and DMAP (1.19 g, 9.75 mmol) and benzyl chloroformate (1.5 g, 8.2 mmol) were added. The resulting solution was stirred at room temperature. When reaction was judged complete by TLC analysis the mixture was partitioned between CH_2Cl_2 and 1M H_3PO_4. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2X). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale oil. Chromatography on silica gel (3:2,

hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethoxycarbonyl)pyrrolidine as a white solid (1.34 g, 40%). m.p. 85 °C. Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.81; H, 6.94; N, 2.99.

Example 54

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylethoxycarbonyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_3$; R^4 = H; R^5 = $-CO_2CH(CH_3)_2$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine (500 mg, 1.57 mmol) in 4 mL of CH_2Cl_2 was added at 0 °C 4-dimethylaminopyridine (250 mg, 2.04 mmol), followed by isopropyl chloroformate (1.7 mL of a 1M toluene solution). After 16 hr the reaction was diluted with CH_2Cl_2 and washed with 1M H_3PO_4. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (2:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylethoxycarbonyl)pyrrolidine as a white solid (280 mg, 44%). Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.16; H, 7.69; N, 3.43.

Example 55

3-(3-Cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-methoxycarbonyl-4-methylpyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CO_2CH_2CH_3$; R^4 = CH_3; R^5 = $-CO_2C(CH_3)_3$; R^{12} = methyl)

To a solution of trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-4-methylpyrrolidine (317 mg, 0.90 mmol) in 1.5 mL of CH_2Cl_2 at 0 °C was added 4-dimethylaminopyridine (145 mg, 1.17 mmol), followed by di-t-butyl dicarbonate (259 mg, 1.17 mmol). After 12 hr the reaction was diluted with ether and washed with 1M H_3PO_4. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (5:2, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-ethoxycarbonyl-4-methylpyrrolidine as a viscous oil (358

mg, 87%). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 66.95; H, 8.36; N, 3.06.

Example 56

trans-3-(3-Cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methoxymethyl)pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-CH_2OCH_3$; R^4 = H; R^5 = $-CO_2CH_3$; R^{12} = methyl)

To a solution of trans-3-(-cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(methoxycarbonyl)pyrrolidine (250 mg, 0.72 mmol) and methyl iodide (3.60 mmol, 0.22 mL) in 1.5 mL of THF was added sodium hydride (86.4 mg of 60% oil dispersion, 2.16 mmol). After 10 min an additional 0.22 mL of methyl iodide and 58 mg of sodium hydride were added. After 15 min H_2O was added dropwise until bubbling ceased. The mixture was diluted with CH_2Cl_2 and washed with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3X). The organic layers were dried (K_2CO_3), filtered and concentrated under reduced pressure to an oil. Silica gel chromatography (2:1, hexanes:ethyl acetate) provided trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methoxymethyl)pyrrolidine as a colorless oil (234 mg, 89%). ^{1}H-NMR (300 MHz): δ 3.29 (s, 3), 3.72 (s, 3), 3.83 (s, 3).

Example 57

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(phenylcarbonyl) pyrrolidine:

(R^1 = cyclopentyl; R^2 = H; R^3 = $-COCH_3$; R^4 = $-CH_3$; R^5 = $-CO-C_6H_5$; R^{12}=methyl)

To a cooled (0°C) solution of 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine (350 mg, 1.1. mmol) in CH_2Cl_2 (3 ml) was added 4-dimethylaminopyridine (175 mg, 1-4 mmol), followed by dropwise addition of benzoyl chloride (170 mg. 1.2 mmol). The resulting mixture was allowed to stir at room temperature for 16 hr. and then was diluted with CH_2Cl_2. The solution was washed sequentially with 1 M H_3PO_4 and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a thick oil. Silica gel chromatography (1:1, hexanes: ethylacetate) provided 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(phenylcarbonyl) pyrrolidine as a white foamy solid (361 mg, 78%).

Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32.
Found: C, 74.08; H, 7.43; N, 3.28.

The following compounds were prepared according to the general procedure set forth above in Example 57:

Example 58

3-(3-cyclopentoxy-4-methoxypheny)-1-(4-methoxy phenylcarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine
(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-(4-$CH_3OC_6H_4$); R^{12}=methyl)
Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10.
Found: C, 71.62; H, 7.41; N, 3.05.

Example 59

1-(4-chlorophenylcarbonyl)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine
(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-(4-ClC_6H_4); R^{12}=methyl)
Anal. Calcd for $C_{26}H_{30}ClNO_4$: C, 68.49;H, 6.63; N, 3.07.
Found: C, 68.20; H, 6.59;N, 3.02.

Example 60

3-3-cyclopentoxy-methoxyphenyl)-1-(2-furyl carbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine
(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-(2-furyl); R^{12}=methyl)
Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40.
Found: C, 69.83; H, 7.08; N, 3.38.

Example 61

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(4-iodo phenylcarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-(4-IC_6H_4); R^{12} = methyl)

Example 62

3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethoxycarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-CH_2CH_3; R^{12}=methyl)

To a cooled (0°C) solution of 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine (350 mg, 1.1 mmol) and 4-dimethylaminopyridine (175 mg, 1.4 mmol) was added dropwise ethyl chloroformate (131 mg, 1.2 mmol). The mixture was stirred at room temperature for 16 hours, diluted with CH_2Cl_2 and washed with 1M H_3PO_4 and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. Silica gel chromatography (2:1, hexanes: ethyl acetate provided 3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethoxycarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine as a colorless oil (291 mg, 68%).

Anal. Calcd for C_{22} H_{31} NO_5: C, 67.84; H, 8.02; N, 3.59.
Found: C, 67.68; H, 8.04; N, 3.57.

The following compound was prepared according to the general procedure set forth above in Example 55:

Example 63

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethyl ethoxycarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-$C(CH_3)_3$; R^{12} = methyl)

Anal. Calcd for C_{24} H_{35} NO_5: C, 69.04; H, 8.45; N, 3.36
Found: C, 69.12; H, 8.48, N, 3.40

The following compound was prepared according to the general procedure set forth above in Example 28:

Example 64

3-(3-cyclopentoxy-4-methoxyphenyl)-1-formyl-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-COCH_3$; R^4 = $-CH_3$; R^5 = -CHO; R^{12} = methyl)

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06.
Found: C, 69.43: H, 7.92; N, 3.98

Example 65

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(methylsulfonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = $-COCH_3$; R^4 = $-CH_3$; R^5 = $-SO_2CH_3$; R^{12} = methyl)

To a cooled (0°C) solution of 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine (497 mg, 1.57 mmol), triethylamine (158 mg, 1.72 mmol), and 4-dimethylaminopyridine (19 mg, 0.16 mmol) in CH_2Cl_2 (4.0 ml) was added dropwise methanesulfonyl chloride (189 mg. 1.65 mmol). After addition an additional 3 ml of CH_2Cl_2 was added. The mixture was stirred for 30 minutes and then partitioned between CH_2Cl_2 and 1M H_3PO_4. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil, which solidified on standing. Trituration with methanol provided the title compound 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(methylsulfonyl) pyrrolidine as a tan solid (590 mg, 95%).

Anal. Calcd for $C_{20}H_{29}NO_5S$: C, 60.74; H, 7.39, N, 3.54.
Found: C, 60.54; H, 7.48; N, 3.50.

The following compound was prepared according to the general procedure set forth above in Example 27:

Example 66

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-imidazolyl carbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -CO-(1-imidazolyl); R^{12} = methyl)

Anal. Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21.
Found: C, 66.85; H, 7.15; N, 10.14.

Example 67

1-aminocarbonly-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2 = H; R^3 = -$COCH_3$; R^4 = -CH_3; R^5 = -$CONH_2$; R^{12} = methyl)

To a cooled (0°C) solution of 3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine (500 mg, 1.6 mmol) and 4-dimethylaminopyridine (586 mg, 4.8 mmol) in CH_2Cl_2 (3.2 ml) was added trimethylsilylisocyanate (3.3 ml, 16 mmol). After 3 hours, the cloudy mixture was diluted with CH_2Cl_2 and washed with 1MH_3PO_4 and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to foamy solid. Silica gel chromatography (15:1, CH_2Cl_2: methanol) provided 1-aminocarbonly-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine as a foamy white solid (400 mg, 69%). Elemental analysis calculated with 0.35 mmol H_2O.

The following compound was prepared according to the general procedure set forth above in Example 26:

Example 68

3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine

(R^1 = cyclopentyl; R^2=H; R^3-$COCH_3$; R^4=-CH_3; R^5=-$COCH_2$ CH_3; R^{12}=methyl)

Anal. cald. for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75.
Found: C, 70.86; H, 8.41; N, 3.80

Compounds of Formula (I) which contain acidic moieties may form pharmaceutically acceptable salts with suitable cations. Suitable pharmaceutically acceptable cations include alkali metal (e.g., sodium or potassium) and alkaline earth metal (e.g., calcium or magnesium) cations. In light of the foregoing, any reference to compounds of the present invention appearing herein is intended to include both compounds of Formula (I) as well as pharmaceutically acceptable salts and solvates thereof.

As previously mentioned, the compounds of the present invention are useful for inhibiting PDE-IV activity in a mammal. For example, PDE-IV inhibitors are useful in the treatment of a variety of allergic, autoimmune and inflammatory diseases. Inflammation is a localized, protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off (sequester) both the injurious agent and the injured tissue (see Dorland's Medical Dictionary). The term "inflammatory disease", as set forth herein, is intended to mean any disease in which an excessive or unregulated inflammatory response leads to excessive inflammatory symptoms, host tissue damage or loss of tissue function. Additionally, the term "autoimmune disease", as set forth herein, is intended to mean any group of disorders in which tissue injury is associated with humoral or cell-mediated responses to the body's own constutuents (Id.). The term "allergic disease" is intended to mean any symptoms, tissue damage or loss of tissue function resulting from allergy (a hypersensitive state of the immune system brought about by exposure to a particular substance which biochemically interacts with an organism resulting in a change in the organism's capacity to immunologically react with the substance) (Id.). The term "arthritic disease" is intended to mean any of a large family of diseases all of which are characterized by inflammatory lesions of the joints attributable to a variety of etiologies. The term "dermatitis" is intended to mean any of a large family of diseases of the skin which are characterized by inflammation of the skin attributable to a variety of etiologies (Id.). The term "transplant rejection", as set forth herein, is intended to mean any immune reaction directed against grafted tissue [including organ and cell (e.g., bone marrow)] and characterized by a loss of function of the grafted and surrounding tissues, pain, swelling, leukocytoisis and thrombocytopenia (Id.).

The present invention also provides a method for modulating cAMP levels in a mammal as well as a method for treating diseases characterized by elevated cytokine levels.

The term "cytokine", as set forth herein, is intended to mean any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a monocyte however many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNFα) and Tumor Necrosis Factor beta (TNFβ).

Additionally, the present invention provides a method for reducing TNF levels in a mammal which comprises administering an effective amount of a compound of Formula (I). The term "reducing TNF levels" , as set forth herein, is intended to mean either:

a) decreasing excessive in vivo TNF levels in a mammal to normal levels or below normal levels by inhibition of the in vivo release of TNF by all cells, including but not limited to monocytes or macrophages; or

b) inducing a down regulation, at the translational or transcription level, of excessive in vivo TNF levels in a mammal to normal levels or below normal levels; or

c) inducing a down regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

Moreover, the compounds of the present invention are useful in suppressing inflammatory cell activation. The term "inflammatory cell activation", as set forth herein, is intended to mean the induction by a stimulus (including but not limited to cytokines, antigens or auto-antibodies) of a proliferative cellular response, the production of soluble mediators (including but not limited to cytokines, oxygen radicals, enzymes, prostanoids, or vasoactive amines), or cell surface expression of new or increased numbers of mediators (including but not limited to major histocompatability antigens or cell adhesion molecules) in inflammatory cells (including but not limited to monocytes, macrophages, T lymphocytes, B lymphocytes, granulocytes, polymorphonuclear leukocytes, mast cells, basophils, eosinophils and endothelial cells). It will be appreciated by those schooled in the art

that the activation of one or a combination of these phenotypes in these cells can contribute to the initiation, perpetuation or exacerbation of an inflammatory condition.

Furthermore, the compounds of the present invention are useful in causing airway smooth muscle relaxation (see Giebycz and Barnes, Biochem Pharmacol 42:663, 1991), bronchodilation (see Heaslip er al, J Pharmac exp Ther 257:741, 1991) and prevention of bronchoconstriction (see Small, et al, Eur J Pharmacol 192:417, 1991; Giebycz and Barnes, Biochem Pharmacol 42:663, 1991).

Some examples of diseases for which the compounds of the present invention are useful in treating include arthritic diseases such as rheumatoid arthritis, osteoarthritis, gouty arthritis and spondylitis. Examples of other such diseases include sepsis, septic shock, endotoxic shock, gram negative sepsis, gram positive sepsis, toxic shock syndrome, asthma, chronic bronchitis, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, reperfusion injury of the myocardium, brain or extremities, fibrosis including cystic fibrosis, keloid formation, scar formation, atherosclerosis, autoimmune diseases such as lupus erythematosus and transplant rejection disorders (e.g. graft vs. host reaction and allograft rejection), chronic granulonephritis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis and inflammatory dermatoses such as atopic dermatitis, psoriasis or urticaria.

Other examples of such diseases or related conditions include pyrexia, cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), AIDS, cerebral malaria, osteoporosis and bone resorption diseases, keloid formation, scar tissue formation and fever and myalgias due to infection. In addition, the compounds of the present invention are useful in the treatment of diabetes insipidus and central nervous system disorders, such as depression and multi-infarct dementia.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses

employed for adult human treatment will typically be in the range of .001 mg/kg to about 100 mg/kg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compounds of the present invention are conveniently administered in unit dosage forms, for example, containing 10 to 1500mg, conveniently 20 to 1000mg, and most conveniently 50 to 700mg of active ingredient per unit dosage form.

While it is possible for use in therapy that a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention therefore further provides a pharmaceutical formulation comprising a compound of Formula (I) or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may be conveniently presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient as a powder or in granules or as a solution, a suspension or an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents. The tablets may be coated according to methods known in the art. Oral liquid preparations may be in the form of, for example,

aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils) or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and may contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents or coloring agents.

Examples of formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Examples of pharmaceutical formulations suitable for rectal administration include forms wherein the carrier is a solid, most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Examples of formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

In examples of formulations suitable for administration by inhalation or insufflation, the compounds may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will generally be aqueous for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, polyethlene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients such as preservatives (e.g. benzalkonium chloride), solubilising agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

Administration by inhalation may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC). Such propellants include, for example, dichlorodifluoromethane, trichlorofluoromethane or, dichlorotetrafluroroethane, 1,1,1,2-tetrafluoroethane (P134a), 1,1,1,2,3,3,3-heptafluoropropane (P227), carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by providing a metered valve.

Alternatively the compounds may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form such as capsules or cartridges of, for example, gelatin or blister packs from which the powder may be administered by means of an inhaler.

Formulations of the present invention may be administered in standard manner for the treatment of the indicated diseases, such as orally, parenterally, sublingually, transdermally, rectally, via inhalation or via buccal administration. For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients such as binding agents, (for example, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulphate. The tablets may be coated according to methods well-known in the art.

The biological activity of the compounds of Formula (I) was evaluated according to the following protocols with appropriate data provided below.

EXPERIMENTAL

Cloning and expression of human recombinant PDE-IV

In order to obtain large quantities of cyclic AMP-specific Type IV phosphodiesterase (PDE-IV) protein to screen inhibitors, the cloning and expression of a human PDE-IV (hPDE-IV) from myelocytic lineage cells was performed. Previous PDE activity data has shown that dibutyryl cyclic AMP (dbcAMP)-differentiated HL-60 cells (ATCC,CCL 240; Verghese, M. unpublished results). Therefore, a cDNA library constructed from dbcAMP-treated HL 60 mRNA was screened to isolate a PDE-IV clone.

A lambda gt10 dibutyryl cAMP-stimulated HL-60 cDNA library (obtained from Dr. R. Snyderman, Duke University Medical Center) was screened first by the polymerase chain reaction (PCR) technique (see "PCR Protocols, A guide to Methods and Application" Eds. Innis, M.A. et al., Academic Press Inc. (1990) with rat PDE-IV primers in order to obtain partial hPDE-IV sequence. Three sets of sense and antisense primers were made to the conserved region of PDE-IV from rat (Colicelli, J., et al., PNAS 86:3599 (1989), Swinnen, J.V., et al., PNAS 86:5325 (1989)). The primers were used in various combinations to amplify a set of PCR fragments and show that the library contained PDE-IV inserts. The resulting PCR fragments were subcloned and sequenced (Sanger, F., et al., PNAS 74:5463 (1977) and found to contain extensive homology with the kPDE-IV sequence from rat. Two of the

primers from the primer sets that were found to have 100% homology with sequence from the PCR fragments were used to screen the cDNA library.

Two cDNA clones, hPDE-R and PDE-M, were obtained by conventional hybridization screening (in "Molecular Cloning, A Laboratory Manual" Volume 2, Eds. Sambrook, J., et al., Cold Spring Harbor Laboratory Press (1989)) of the HL-60 cDNA library. The cDNA inserts of hPDE-M and hPDE-R were subcloned into M13mp18a (Messing J., Methods of Enzymology, 101:20 (1983)) and sequenced. Sequence analysis showed regions of perfect homology between hPDE-M and hPDE-R with divergent sequences at both the 5' and 3' ends (see Figure 1). These cDNAs also had regions of extensive homology with the rat PDE-IV. Analysis of all the sequence information from both clones hPDE-R and hPDE-M resulted in the identification of an open reading frame of 1462 bases which should code for a protein of approximately 55 kD.

In particular, Fig. 1 sets forth the EcoRI cDNA inserts from the Lambda gt10 cDNA library, identified as hPDE-M and hPDE-R. These were subcloned into M13, generating the constructs M13mp18a PDE-M and M13mp18a PDE-R, and sequenced. Sequence analysis found regions of perfect homology between hPDE-M and hPDE-R (hatched box) with divergent sequences at both the 5' and 3' ends. Clone hPDE-R started internally in the coding region, diverged from PDE-M (open box), contained a stop codon (TAA), and ended with a 3' untranslated region (thin bar). Clone PDE-M began with an intron, contained an internal intron (loop), as well as a 3' region that diverged from PDE-R and is a potential intron (bold box and bar). PDE-M also contained a continuation of the coding sequence (checkered box). An in-frame methionine codon (ATG) was located that had stop codons in all three reading frames, 5' to this methionine.

To express this PDE-IV in E. coli, hPDE-M and hPDE-R were modified by site directed mutagenesis in order to join sequences from the 5' region of hPDE-M to the 3' region of hPDE-R (see Figure 2). The restriction fragments were ligated into the pET vector expression system (obtained from Novagen Inc.) which places a coding region under the control of the bacteriophage T7 promoter. The resulting clone, pIP595, and intermediates were characterized by sequence analysis during mutagenesis and assembly. The plasmid, pIP595, yielded a high level of an approximately 55 kD protein, denoted herein as GRI-PDE-IV, which was purified, sequenced and characterized in order to verify that it was an active PDE-IV.

In particular, Fig. 2 illustrates how hPDE-IV was generated by modifying hPDE-M and hPDE-R by site-directed mutagenesis to add restriction sites to assemble hPDE-IV. hPDE-M was modified by adding an NdeI site at the start codon(ATG 441) and an EcoRV site at by 605,5' to the internal intron (see Figure 1). hPDE-R was modified by adding an EcoRV site at bp 603 and a BamHI site directly 3' to the stop codon at position 1900 bp, 3' of the stop codon (TGA 1890). The EcoRV site was chosen at this position because it could be introduced without altering any amino acids in the translated peptide. The NdeI to EcoRV fragment from hPDE-M and the EcoRV to BamHI fragment from hPDE-R were purified and ligated into the pET vector plasmid pET11b digested with NdeI and BamHI to produce a functional expression construct, pIP595, of hPDE-IV. This construct was used to express hPDE-IV in E.coli. The additional restriction sites EcoRI, SstI, PstI, NcoI, and HindIII, are included. The Amp resistance gene (Amp), the Lac I gene (Lac I), the orgin of replication (ori) and the T7 transcription unit (T7 pro and stippled arrow on plasmid) for pET11b are also shown.

The GRI-PDE-IV protein was also placed into a baculovirus expression system. Site directed mutagenesis was used to make a similar construct as in pIP595 in the vector pJP10Z (Vialard, J., Journal of Virology 64:37 (1990)) used for baculovirus expression (see Figure 3). This vector places a coding region under the control of the polyhedron promoter for constitutive high levels of expression. The resulting clone, pIP596, and intermediates were also characterized by sequence analysis during mutagenesis and assembly. A recombinant baculovirus was obtained after co-transfection of the pIP596 construct with wild type virus. This recombinant virus was used to express large amounts of this protein in SF9 insect cells.

In particular, Fig. 3 illustrates how hPDE-IV was generated by modifying hPDE-M and hPDE-R as in Fig. 2 by site-directed mutagenesis to add restriction sites to assemble hPDE-IV for baculovirus expression. hPDE-M was modified by adding an NheI site at the start codon and an EcoRV site at bp 605, 5' to the internal intron. hPDE-R was modified by adding an EcoRV site at bp 603 and a NheI site directly 3' to the stop codon. The NheI to EcoRV fragment from hPDE-M and the EcoRV to NheI fragment from hPDE-R were ligated into the baculovirus vector plasmid pJVP10Z digested with NheI to produce the construct pIP596 of hPDE-IC. This construct was used to co-transfect SF9 insect cells along with wild type baculovirus to generate recombinant virus for expression human recombinant PDE-IV (hrPDE-IV). The additional restriction sites EcoRI, SstI, PstI, NcoI, and HindIII, are included. The Amp resistance gene (AMP), the P10 promoter and the Lac Z gene (P10

Promoter, Lac Z), the origin of replication (ori), and the Polyhedron transcription unit (Polyhedron Promoter and stippled arrow on plasmid) for pJVP10Z are also shown.

hrPDE-IV activity assay and assay for hrPDE-IV inhibition

The following assay was employed to assess the ability of the compounds of the invention to inhibit hrPDE IV. Baculovirus expressed hrPDE-IV was assayed using a modified version of the coupled enzyme protocol described by Kono. See Kono, T. (1984) in Methods in Diabetes Research, Vol. I (Larner, J., and Pehl, S. L., eds.), pp. 83-91, John Wiley & Sons, New York. In this assay, hrPDE-IV activity converts [^{3}H]cAMP to [^{3}H]AMP in proportion to the amount of hrPDE-IV activity present. The [^{3}H]AMP is then completely converted to [^{3}H]adenosine by excess 5'-nucleotidase. The amount of [^{3}H]adenosine liberated is therefore directly proporational to the hrPDE-IV activity. [^{14}C]adenosine is used as an internal control. The assay is performed at 30°C in a 50 µl reaction mixture containing: 1mM Tris-HCl (pH 7.5), 1mM $MgCl_2$, 0.1 mM EDTA, 0.33 µg/µl BSA, 0.5 µg 5'-nucleotidase, 0.1 µM ^{3}H-cAMP, 1 µM ^{14}C-Ad, hrPDE IV stock solution, and the desired concentration of test compound. The PDE IV reaction was stopped with 200 µl of a slurry containing 50% Sephadex A-25 and 5mM CAPS (pH 10). The mixture of [^{3}H]adenosine and [^{14}C]adenosine was eluted batchwise from the slurry, the amount of radioactivity is determined and the hrPDE-IV activity is calculated.

The Ki's of compounds set forth in the Examples were determined by measuring the inhibition of cAMP hydrolysis as a function of the concentration of the test compound over the range of 0 to 100 µM. The Ki's of the compounds tested in the aforementioned assay ranged from about 100pM to about 20µM.

Assay for binding to hrPDE-IV

The binding of [^{3}H]rolipram to hrPDE-IV was assessed using a modified version of the protocol described by Schneider, et al (see Schneider, et al, Eur J Pharmacol 127:105, 1986). hrPDE IV is incubated with [^{3}H]rolipram (e-9M final) and test compounds (e-11 thru e-4M) in a volume of 1.0 mL containing (mM): NaCl (100), Tris-HCl (25), MgCl2 (10), CaCl2 (1) dithiothreitol (1) and BSA (0.25%) pH 7.4. Reaction termination: brain homogenate-after 60 min at room temperature the reaction mixture is filtered onto polyethyleneimine treated (0.3%, >3 hours) glass fiber filters; recombinant PDE IV-after 60 min on ice, hydroxyapatite is added (final HAP is 2.5% w/v) with vigorous mixing to adsorb the ligand/receptor complex prior to filtration onto glass fiber filters as described above. Radioactivity is quantitated by

liquid scintillation counting. IC50 values for test compound competition for rolipram binding are estimated from concentration/response curves and converted to Ki values using the Cheng-Prusoff correction. The Ki's of the compounds tested in the aforementioned assay ranged from about 1nM to about 20μM.

Assay for inhibition of LPS-induced TNFα production

In order to assess the ability of a compound to reduce TNFα secretion in elicited mouse peritoneal macrophages, the following protocol was employed. It will be appreciated by those skilled in the art that previous studies have demonstrated that incubation of human or mouse monocytes with cAMP elevating agents, such as prostaglandin E_2 (PGE_2), forskolin or dbcAMP, inhibit lipopolysaccharide (LPS)-induced secretion of TNFα. (See Scales, W. E., S. W. Chensuc, I. Otterness and S. L. Kunkel, 1989, Regulation of monokine gene expression: Prostaglandin E_2 suppresses tumor necrosis factor but not interleukin-1a or b-mRNA and cell-associated bioactivity, J. Leukocytc Biology 45:416-421.). (See also Renz, H., J-H. Gong, A. Schmidt, M. Nain and Diethard Gemsa, 1988, Release of tumor necrosis factor-a from macrophages. Enhancement and suppression are dose-dependently regulated by prostaglandin E_2 and cyclic nucleotides, J. Immunol. 141:2388-2393). Accordingly, preliminary experiments were performed to demonstrate that rolipram, a type IV specific phosphodiesterase inhibitor, inhibited LPS induced TNFα secretion from murine macrophages. (See Noel, L. S., M. Verghese, K. M. Connolly, L. J. Sekut and S. A. Stimpson, 1992, Type IV-specific phosphodiesterase (PDE) inhibitors suppress murine TNFα expression in vitro and in vivo--(abstract)--6th International Conference, Inflammation Research Association). TNFα secretion from murine elicited peritoneal macrophages was used as a readout for a compound's ability to raise cAMP, and/or inhibit phosphodiesterase within a cell.

Mice (female C3H mice, 15-20 gm body weight) were injected intraperitoneally with 2 mL of 5mM sodium periodate solution. Five days later, animals were sacrificed under CO_2 and the cells recovered as follows. Ten mL of cold phosphate buffered saline (PBS) was injected into the peritoneal cavity, the abdomen massaged, and fluid recovered. Cells were washed 2 times with cold PBS containing 5mM EDTA, centrifuged at 1100 X g for 7 min and resuspended in warm RPMI medium (GIBCO RPMI Medium 1604 containing 25mM HEPES, L-glutamine, 1% Hyclone fetal bovine serum, penicillin and streptomycin) at a concentration of 5×10^5 cells/mL. One mL of cells was placed into each well of a 24-well tissue culture plate. Cells were incubated 2 to 2.5 hours at 37°C under 7% CO_2. Wells were gently washed 2 times

with warm PBS, without EDTA. The remaining, adherent cells are approximately 95% macrophages. Compounds were dissolved in dimethylsulfoxide (DMSO) to a concentration of 10mM. These stock solutions were then diluted into RPMI medium. Compounds were added to wells approximately 10 min. before LPS addition (the time necessary to prepare and add LPS). DMSO similarly diluted in medium was used as a negative control. Cells were cultured 16 hours at 37°C, 7% CO_2. Following incubation, 0.7 mL of supernatant was removed to polypropylene tubes for TNFα measurement. TNFα protein in the supernatant fluids was measured using a commercially available enzyme-linked immunosorbant assay (ELISA) (Genzyme).

Assay for inhibition of serum TNFα levels in mammals.

In order to assess the ability of a compound to reduce serum TNFα levels in mammals, the following protocol was employed. It will be appreciated by those skilled in the art that previous studies have demonstrated that incubation of LPS-activated human monocytes with agents that can elevate cAMP, like PGE2, forskolin and dbcAMP, inhibited secretion of TNFα. PDE-IV inhibitors like rolipram, which also elevate cAMP, have been found to inhibit serum TNFα as well. Rolipram has also been found to inhibit secretion of TNFα from LPS-activated mouse macrophages. Accordingly, in vivo efficacy of a PDE-IV reducing compound was shown by dosing with compound and measuring reduction of serum TNFα levels in LPS-injected mice. Female C3H mice, 20-25 gm body weight were fasted overnight and dosed orally with test compound in appropriate vehicle 30 minutes before LPS injection. Five μg of LPS was then injected intraperitoneally into the mice. Exactly 90 minutes after LPS injection, mice were bled from the heart. Blood was allowed to clot overnight at 4° C. Samples were centrifuged for 10 minutes in a micro centrifuge and the serum removed and stored at -20°C until analysis. Serum levels of TNFα were subsequently measured using a commercially available ELISA kit (Genzyme) following the protocol enclosed in the kit. The percent of inhibition of serum TNFα levels caused by the compound was determined relative to serum TNFα levels in control mice receiving vehicle alone.

Assay for inhibition of experimental arthritis in rats.

The ability of a compound to inhibit experimental arthritis in rats was determined using the reactivation of peptidoglycan-polysaccharide (PG-PS)-induced monarthritis model (see Stimpson, S. A., and J. H. Schwab, 1989, Chronic remittent erosive arthritis induced by bacterial peptidoglycan-polysaccaride structures, as referenced in Pharmacological Methods in the Control of Inflammation, J. Chang and A. S.

Lewis, eds., Alan R. Liss, Inc., New York, pp. 381-394). The following protocol was employed. PG-PS was purified from group A streptococcal cell walls by exhaustive extraction with detergents, sonicated and fractionated by differential centrifugation. PG-PS fragments sedimenting at 100,000 x g, but not at 10,000 x g, were used (PG-PS 100P fraction). The rhamnose content of the PG-PS 100P was determined by standard colorimetric assay for methylpentose (see Dische and Shettles, J Biol Chem 175:590, 1948). All PG-PS doses were based on rhamnose equivalent. Female Lewis rats (ca. 150 g) were primed in the right ankle with an intraarticular injection of 2.5 µg PG-PS 100P. This causes an acute inflammatory reaction which peaks within 24 hours and gradually wanes, leaving a mild chronic inflammation of the ankle. Two weeks later (day 0), rats are injected intravenously with 150 µg PG-PS 100P. This induces a reactivation of arthritis in the primed ankles which peaks in severity in 48 to 72 hours. This reactivation of arthritis is quantified by determining the increase in swelling of the ankle joint immediately before to 48 hours after the intravenous PG-PS injection. Compounds in an appropriate vehicle (usually methyl cellulose or cottonseed oil) are administered orally at -1, 6,24 and 30 hours relative to the intravenous PG-PS injection. Joint swelling is measured at 48 hours and % inhibition caused by the comound is determined relative to control arthritic rats which were treated with vehicle alone.

The following are examples of suitable formulations of compounds of the invention. The term "active ingredient" is used herein to represent a compound of the invention.

Tablets

These may be prepared by normal methods such as wet granulation or direct compression.

A. Direct Compression	mg/tablet
Active ingredient	2.0
Microcrystalline Cellulose USP	196.5
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to microcrystalline cellulose or the compression weight and using suitable punches.

B. Wet Granulation	mg/tablet
Active ingredient	2.0
Lactoss BP	151.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium StearateBP	1.5
Compression	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using suitable punches.

C. For Buccal Administration	mg/tablet
Active ingredient	2.0
Lactose BP	94.8
Sucrose BP	86.7
Hydroxypropylmethylcellulose	15.0
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with the lactose, sucrose and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using suitable punches.

The tablets may be film coated with suitable film forming materials, such as hydroxypropylmethylcellulose, using standard techniques. Alternatively, the tablets may be sugar coated.

Capsules	mg/capsule
Active ingredient	2.0
Starch 1500*	97.0
Magnesium Stearate BP	1.0
Fill Weight	100.0

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and, if necessary, changing to a suitable capsule size.

Syrup

This may be either a sucrose or sucrose-free presentation.

A. Sucrose Syrup	mg/5ml dose
Active ingredient	2.0
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer)	
Flavour)	as required
Colour)	
Preservative)	
Purified Water BP to	5.0ml

The active ingredient, buffer, flavor, color and preservative are dissolved in some of the water and glycerine is added. The remainder of the water is heated to dissolve

the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup produced is clarified by filtration.

B. Sucrose-Free	mg/5ml dose
Active ingredient	2.0mg
Hydroxypropyl methylcellulose USP (Viscosity type 4000)	22.5mg
Buffer)	
Flavour)	
Colour)	as required
Preservative)	
Sweetener)	
Purified Water BP to	5.0ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

Metered Dose Pressurised Aerosol

A. Suspension Aerosol	mg/metered dose	per can
Active ingredient micronised	0.100	13.20mg
Oleic Acid BP	0.010	2.64mg
Trichlorofluoromethane BP	23.64	5.67mg
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronized in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10 - 15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves delivering 85mg of suspension are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

B. Solution Aerosol	mg/metered dose	per can

Active ingredient	0.055	13.20mg
Ethanol BP	11.100	2.66g
Dichlorotetrafluoroethane BP	25.160	6.04g
Dichlorodifluoromethane BP	37.740	9.06g

Oleic acid BP, or a suitable surfactant, e.g. Span 85 (sorbitan trioleate) may also be included.

The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by dichlorotetrafluoroethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Injection for Intravenous Administration	mg/ml
Active ingredient	0.5mg
Sodium chloride BP	as required
Water for Injection BP to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilized by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilized by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Inhalation Cartridges	mg/cartridge
Active ingredient micronised	0.200
Lactose BP to	25.0

The active ingredient is micronized in a fluid energy mill to a fine particular size range prior to blending with normal tablet grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating

machine. The contents of the cartridges are administered using a powder inhaler, such as the Glaxo Rotahaler.

Suppositories

Active ingredient	2.0mg
Witepsol H15*	1.0g

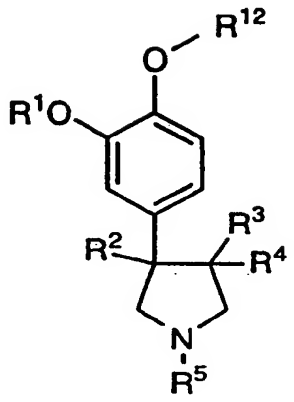
* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

CLAIMS:

We claim:

1. A compound of Formula (I)



(I)

wherein:

R^1 is alkyl, haloalkyl, cycloalkyl, bridged polycycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl or aryloxyalkyl;

R^2 is H, alkyl, haloalkyl, cycloalkyl, aryl, -CO-alkyl, -CO-cycloalkyl, -CO-aryl, -COO-alkyl, -COO-cycloalkyl, -COO-aryl, CH_2OH, CH_2-O-alkyl, -CHO, -CN, $-NO_2$ or SO_2R^{10};

R^3 is -CO-alkyl, -CO-haloalkyl, -CO-cycloalkyl, -COO-alkyl, -COO-cycloalkyl, -COOH, -CO-aryl, $-CONR^6R^7$, $-CH_2OH$, $-CH_2O$-alkyl, -CHO, -CN, $-NO_2$, $-NR^8COR^9$, $-NR^8SO_2R^{10}$ or $-SO_2R^{10}$;

R^4 is H, alkyl, haloalkyl, cycloalkyl, -CO-alkyl, -CO-haloalkyl, -CO-cycloalkyl, -COO-alkyl, -COO-cycloalkyl, -COOH, -CO-aryl, $-CONR^6R^7$, -CN, -CHO or SO_2R^{10};

R^5 is -CN or $-C(X)-R^{11}$ or SO_2R^{10};

R^6 and R^7 are independently selected from H, alkyl, cycloalkyl, aryl or aralkyl or R^6 and R^7 together form a 4- to 7-membered heterocyclic or carbocyclic ring;

R^8 is H, alkyl or cycloalkyl;

R^9 is alkyl, cycloalkyl, aryl, alkoxy, aralkoxy or $-NR^6R^7$;

R^{10} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl or $-NR^6R^7$;

R^{11} is H, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heteroaryl, C_{1-6}alkoxy, aralkoxy, aryloxy or $-NR^6R^7$;

R^{12} is C_{1-3}alkyl, cyclopropyl or C_{1-3}haloalkyl; and

X is O or S.

2. A compound according to Claim 1 wherein R^{12} is methyl.

3. A compound according to Claim 2 wherein R^5 is $-C(X)-R^{11}$ and X is O.

4. A compound according to Claim 3 wherein R^1 is further selected from alkyl, cycloalkyl, bridged polycycloalkyl, aryl, aralkyl, heteroaralkyl or aryloxyalkyl.

5. A compound according to Claim 4 wherein R^1 is further selected from alkyl, cycloalkyl, bridged polycycloalkyl, aralkyl, heteroaralkyl or aryloxyalkyl.

6. A compound according to Claim 5 wherein R^1 is further selected from alkyl, cycloalkyl, bridged polycycloalkyl, aralkyl or aryloxyalkyl.

7. A compound according to Claim 7 wherein R^1 is further selected from alkyl, cycloalkyl, aralkyl or aryloxyalkyl.

8. A compound according to Claim 3 wherein R^2 is further selected from H, alkyl, cycloalkyl, -CO-alkyl, -CO-cycloalkyl, -CO-aryl, -COO-alkyl, -COO-cycloalkyl, -COO-aryl, -CN or SO_2R^{10}.

9. A compound according to Claim 3 wherein R^4 is further selected from H, alkyl, cycloalkyl, -CO-alkyl, -CO-cycloalkyl, -COO-alkyl, -COO-cycloalkyl, -COOH, $-CONR^6R^7$, -CN or SO_2R^{10}, provided that when R^2 is -COO-alkyl, -COOH, -CO-alkyl or -CO-aryl, R^4 is H.

10. A compound according to Claim 3 wherein R^9 is further selected from alkyl, cycloalkyl, alkoxy or aralkoxy.

11. A compound according to Claim 1 wherein:

R^1 is alkyl, cycloalkyl, aralkyl or aryloxyaryl;

R^2 is hydrogen;

R^3 is -CO-alkyl, -COO-alkyl, -COOH, -CO-aryl, $-CONR^6R^7$, -CN, $-NO_2$, $-NR^8COR^9$ or $-NR^8SO_2R^{10}$;

R^4 is hydrogen, alkyl or -CO-alkyl;

R^5 is CN or $C(X)R^{11}$; and

R^{12} is C_{1-3}alkyl.

12. A compound according to Claim 1 wherein:

R^1 is cycloalkyl,

R^2 is hydrogen;

R^3 is COalkyl, CO_2H or CO_2alkyl;

$R^4$is hydrogen or methyl;

R^5 is CO_2alkyl; and,

R^{12} is C_{1-3}alkyl.

13. A compound according to Claim 1 wherein:

R^1 is further selected from alkyl, cycloalkyl, aralkyl or aryloxyalkyl;

R^2 is further selected from H, -COO-alkyl, -COO-cycloalkyl or SO_2R^{10};

R^4 is further selected from H, alkyl, cycloalkyl or SO_2R^{10};

R^5 is $-C(X)-R^{11}$;

R^6 and R^7 are further independently selected from H or alkyl;

R^8 is H, alkyl or cycloalkyl;

R^9 is alkyl; and

R^{10} is further selected from alkyl, trifluoromethyl or aryl;

R^{11} is further selected from H, alkyl, heteroaryl, C_{1-6}alkoxy, aralkoxy or $-NR^6R^7$;

R^{12} is methyl; and

X is O.

14. A compound according to Claim 1 wherein the compound is selected from one of the following:

cis-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-methoxycarbonyl-1-(1,1-dimethylethoxycarbonyl)-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-(3,4-dimethoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-(hydroxymethyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-hydroxymethyl-1-(methoxycarbonyl)pyrrolidine;

trans-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

cis-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

trans-1-methoxycarbonyl-3-methoxycarbonyl-4-(3-phenylmethoxy-4-methoxyphenyl)pyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-methyl-4-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-(methoxycarbonyl)pyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-4-(1,1-dimethylethoxycarbonyl)-1-methoxycarbonyl-4-methylpyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethylcarbonyl-1-(methoxycarbonyl)pyrrolidine;

trans-1-methoxycarbonyl-3-nitro-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-cyano-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-nitropyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(phenylcarbonyl)pyrrolidine;

trans-1-methoxycarbonyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-methoxycarbonyl-4-methylpyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-methoxycarbonyl-4-methylpyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylcarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-imidazolylcarbonyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-formyl-4-(methoxycarbonyl)pyrrolidine;

trans-1-formyl-3-methoxycarbonyl-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(1-methylethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-ethoxycarbonyl-1-(methoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-methylethoxycarbonyl)pyrrolidine;

trans-3-carboxy-1-(methoxycarbonyl)-4-[3-(3-phenoxypropoxy)-4-methoxyphenyl]pyrrolidine;

trans-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)-1-formylpyrrolidine;

trans-1-aminocarbonyl-3-carboxy-4-(3-cyclopentoxy-4-methoxyphenyl)pyrrolidine;

trans-3-aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-aminocarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-[(*N*-phenylmethyl)aminocarbonyl]pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-[*N*-(1,1-dimethylethoxycarbonyl)-*N*-methyl]-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(methylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-(phenylmethoxycarbonyl)-4-*N*-(trifluoromethylsulfonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(phenylsulfonyl)-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxy)phenyl)-1-methoxycarbonyl-4-N-(methoxycarbonyl)pyrrolidine;

trans-1-aminocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-*N*-(1,1-dimethylethoxycarbonyl)pyrrolidine;

trans-1-aminothiocarbonyl-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

trans-1-cyano-3-(3-cyclopentoxy-4-methoxyphenyl)-4-(methoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(phenylmethoxycarbonyl)pyrrolidine;

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methoxycarbonyl-1-(methylethoxycarbonyl)pyrrolidine;

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethylethoxycarbonyl)-4-methoxycarbonyl-4-methylpyrrolidine; and

trans-3-(3-cyclopentoxy-4-methoxyphenyl)-1-methoxycarbonyl-4-(methoxymethyl)pyrrolidine.

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(phenylcarbonyl) pyrrolidine:

3-(3-cyclopentoxy-4-methoxypheny)-1-(4-methoxy phenylcarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

1-(4-chlorophenylcarbonyl)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-3-cyclopentoxy-methoxyphenyl)-1-(2-furyl carbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(4-iodo phenylcarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethoxycarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1,1-dimethyl ethoxycarbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-formyl-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-methylcarbonyl-1-(methylsulfonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-(1-imidazolyl carbonyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

1-aminocarbonly-3-(3-cyclopentoxy-4-methoxyphenyl)-4-methyl-4-(methylcarbonyl) pyrrolidine

3-(3-cyclopentoxy-4-methoxyphenyl)-1-ethylcarbonyl-4-methyl-4-(methylcarbonyl) pyrrolidine.

15. A method of treating a mammal for inflammatory diseases comprising administering to said mammal an effective amount of a compound according to Claim 1.

16. A method of treating a mammal for arthritic diseases including osteoarthritis and rheumatoid arthritis which comprises administering to said mammal an effective amount of a compound according to Claim 1.

17. A method of treating a mammal for sepsis, septic shock, endotoxic shock and gram negative or gram positive sepsis or toxic shock syndrome which comprises administering to said mammal an effective amount of a compound according to Claim 1.

18. A method of treating a mammal for adult respiratory distress syndrome, chronic pulmonary inflammatory disease, asthma, silicosis or pulmonary sacroidosis which comprises administering to said mammal an effective amount of a compound according to Claim 1.

19. A method according to Claim 18 further comprising selectively treating said mammal for asthma.

20. A method of treating a mammal for autoimmune diseases including lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis and transplant rejection which comprises administering to said mammal an effective amount of a compound according to Claim 1.

21. A method of treating a mammal for diseases characterized by elevated cytokine levels which comprises administering to said mammal an effective amount of a compound according to Claim 1.

22. A method of treating a mammal for diabetes insipidus which comprises administering to said mammal an effective amount of a compound according to Claim 1.

23. A method of treating a mammal for osteoporosis which comprises administering to said mammal an effective amount of a compound according to Claim 1.

24. A method of treating a mammal for cancer which comprises administering to said mammal an effective amount of a compound according to Claim 1.

25. A method of treating a mammal for AIDS and ARC which comprises administering to said mammal an effective amount of a compound according to Claim 1.

26. A method for suppressing inflammatory cell activation in a mammal comprising administering to said mammal an effective amount of a compound according to Claim 1.

27. A method of reducing TNF levels in a mammal comprising administering to said mammal an effective amount of a compound according to Claim 1.

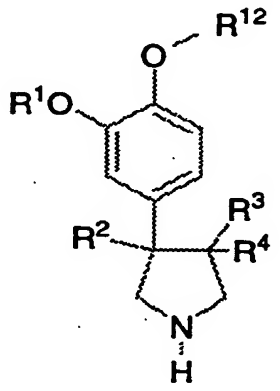
28. A method of inhibiting phosphodiesterase Type IV function in a mammal comprising administering to said mammal an effective amount of a compound according to Claim 1.

29. A method for modulating cAMP levels in a mammal comprising administering to said mammal an effective amount of a compound according to Claim 1.

30. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptible carrier.

31. A process for the preparation of a compound of Formula (I) as defined in Claim 1 which process comprises:

(A) Reaction of a compound of Formula (II)



(II)

with a reagent R^5-Y where Y is an appropriate leaving group; or

(B) Inter conversion of one compound of Formula (I) to another compound of Formula (I).

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 94/10678

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/16 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,87 06576 (PFIZER) 5 November 1987 see page 4, line 17 - line 24 see page 25 ---	1-31
A	JOURNAL OF MEDICINAL CHEMISTRY., vol.32, no.7, 1989, WASHINGTON US pages 1450 - 1457 see the whole document ---	1-31
X	JOURNAL OF ORGANIC CHEMISTRY., vol.58, no.15, 1993, EASTON US pages 3857 - 3868 RN 149894-05-3 REGISTRY CN Pyrrolidine, 3-(3,4-dimethoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-3- (2-methylpropyl)- RN 149894-03-1 REGISTRY CN Pyrrolidine, 3-(3,4-dimethoxyphenyl)-3-ethyl-1-[(4-methylphenyl)sulfonyl]- --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 1995	24. 01. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Kissler, B

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INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 94/10678

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 86, no. 11, 14 March 1977, Columbus, Ohio, US; abstract no. 72427, see abstract & JP,A,5 182 258 (YOSHITOMI) 19 July 1976 ---	1-31
A	WO,A,92 19594 (SMITHKLINE BEECHAM) 12 November 1992 see page 6 - page 8 -----	1-31

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/US 94/10678

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WO-A-8706576	05-11-87	CA-A-	1331606	23-08-94
		DE-D-	3789164	07-04-94
		DE-T-	3789164	09-06-94
		EP-A-	0247725	02-12-87
		ES-T-	2061492	16-12-94
		JP-B-	6045602	15-06-94
		JP-A-	62281864	07-12-87
		SU-A-	1646488	30-04-91
		SU-A-	1653542	30-05-91
JP-A-5182258	23-07-93	NONE		
WO-A-9219594	12-11-92	AU-A-	1917092	21-12-92
		CN-A-	1067244	23-12-92
		EP-A-	0584208	02-03-94
		JP-T-	6507405	25-08-94